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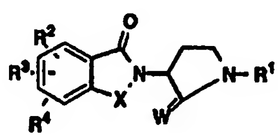

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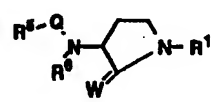

(2)

(57) Abstract

Compounds are provided which inhibit microsomal triglyceride transfer protein and thus are useful for lowering serum lipids and treating atherosclerosis and related diseases. The compounds have structure (1) or (2) wherein $R^1$ to $R^6$, Q, W and X are as defined herein.

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# INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND METHOD

## Field of the Invention

This invention relates to novel compounds which inhibit microsomal triglyceride transfer protein, and to methods for decreasing serum lipids and treating atherosclerosis employing such compounds.

## Background of the Invention

The microsomal triglyceride transfer protein (MTP) catalyzes the transport of triglyceride (TG), cholesteryl ester (CE), and phosphatidylcholine (PC) between small unilamellar vesicles (SUV). Wetterau & Zilversmit, Chem. Phys. Lipids 38, 205-22 (1985). When transfer rates are expressed as the percent of the donor lipid transferred per time, MTP expresses a distinct preference for neutral lipid transport (TG and CE), relative to phospholipid transport. The protein from bovine liver has been isolated and characterized. Wetterau & Zilversmit, Chem. Phys. Lipids 38, 205-22 (1985). Polyacrylamide gel electrophoresis (PAGE) analysis of the purified protein suggests that the transfer protein is a complex of two subunits of apparent molecular weights 58,000 and 88,000, since a single band was present when purified MTP was electro-phoresed under nondenaturing condition, while two bands of apparent molecular weights 58,000 and 88,000 were identified when electrophoresis was performed in the presence of sodium dodecyl sulfate (SDS). These two polypeptides are hereinafter referred to as 58 kDa and 88 kDa, respectively, or the 58 kDa and the 88 kDa component of MTP, respectively, or the low

molecular weight subunit and the high molecular weight subunit of MTP, respectively.

Characterization of the 58,000 molecular weight component of bovine MTP indicates that it is the previously characterized multifunctional protein, protein disulfide isomerase (PDI). Wetterau et al., J. Biol. Chem. 265, 9800-7 (1990). The presence of PDI in the transfer protein is supported by evidence showing that (1) the amino terminal 25 amino acids of the bovine 58,000 kDa component of MTP is identical to that of bovine PDI, and (2) disulfide isomerase activity was expressed by bovine MTP following the dissociation of the 58 kDa - 88 kDa protein complex. In addition, antibodies raised against bovine PDI, a protein which by itself has no TG transfer activity, were able to immunoprecipitate bovine TG transfer activity from a solution containing purified bovine MTP.

PDI normally plays a role in the folding and assembly of newly synthesized disulfide bonded proteins within the lumen of the endoplasmic reticulum. Bulleid & Freedman, Nature 335, 649-51 (1988). It catalyzes the proper pairing of cysteine residues into disulfide bonds, thus catalyzing the proper folding of disulfide bonded proteins. In addition, PDI has been reported to be identical to the beta subunit of human prolyl 4-hydroxylase. Koivu et al., J. Biol. Chem. 262, 6447-9 (1987). The role of PDI in the bovine transfer protein is not clear. It does appear to be an essential component of the transfer protein as dissociation of PDI from the 88 kDa component of bovine MTP by either low concentrations of a denaturant (guanidine HCl), a chaotropic agent (sodium perchlorate), or a nondenaturing detergent (octyl glucoside) results in a loss of transfer

activity. Wetterau et al., Biochemistry 30, 9728-35 (1991). Isolated bovine PDI has no apparent lipid transfer activity, suggesting that either the 88 kDa polypeptide is the transfer protein or that it confers transfer activity to the protein complex.

The tissue and subcellular distribution of MTP activity in rats has been investigated. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). Lipid transfer activity was found in liver and intestine. Little or no transfer activity was found in plasma, brain, heart, or kidney. Within the liver, MTP was a soluble protein located within the lumen of the microsomal fraction. Approximately equal concentrations were found in the smooth and rough microsomes.

Abetalipoproteinemia is an autosomal recessive disease characterized by a virtual absence of plasma lipoproteins which contain apolipoprotein B (apoB). Kane & Havel in The Metabolic Basis of Inherited Disease, Sixth Edition, 1139-64 (1989). Plasma TG levels may be as low as a few mg/dL, and they fail to rise after fat ingestion. Plasma cholesterol levels are often only 20-45 mg/dL. These abnormalities are the result of a genetic defect in the assembly and/or secretion of very low density lipoproteins (VLDL) in the liver and chylomicrons in the intestine. The molecular basis for this defect has not been previously determined. In subjects examined, triglyceride, phospholipid, and cholesterol synthesis appear normal. At autopsy, subjects are free of atherosclerosis. Schaefer et al., Clin. Chem. 34, B9-12 (1988). A link between the apoB gene and abetalipoproteinemia has been excluded in several families. Talmud et al., J.

Clin. Invest. 82, 1803-6 (1988) and Huang et al., Am. J. Hum. Genet. 46, 1141-8 (1990).

Subjects with abetalipoproteinemia are afflicted with numerous maladies. Kane & Havel, supra. Subjects have fat malabsorption and TG accumulation in their enterocytes and hepatocytes. Due to the absence of TG-rich plasma lipoproteins, there is a defect in the transport of fat-soluble vitamins such as vitamin E. This results in acanthocytosis of erythrocytes, spinocerebellar ataxia with degeneration of the fasciculus cuneatus and gracilis, peripheral neuropathy, degenerative pigmentary retinopathy, and ceroid myopathy. Treatment of abetalipoproteinemic subjects includes dietary restriction of fat intake and dietary supplementation with vitamins A, E and K.

In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes. Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). The ability of MTP to catalyze the transport of TG between membranes is consistent with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in the endoplasmic reticulum (ER) membrane to nascent lipoprotein particles within the lumen of the ER.

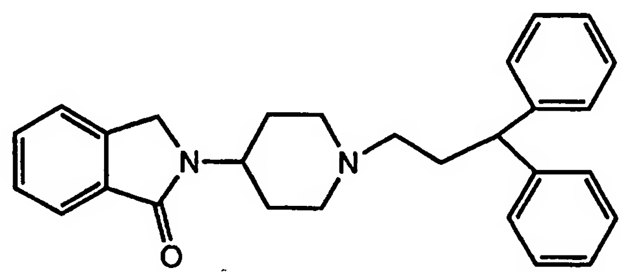
Olofsson and colleagues have studied lipoprotein assembly in HepG2 cells. Bostrom et al., J. Biol. Chem. 263, 4434-42 (1988). Their

results suggest small precursor lipoproteins become larger with time. This would be consistent with the addition or transfer of lipid molecules to nascent lipoproteins as they are assembled. MTP may play a role in this process. In support of this hypothesis, Howell and Palade, J. Cell Biol. 92, 833-45 (1982), isolated nascent lipoproteins from the hepatic Golgi fraction of rat liver. There was a spectrum of sizes of particles present with varying lipid and protein compositions. Particles of high density lipoprotein (HDL) density, yet containing apoB, were found. Higgins and Hutson, J. Lipid Res. 25, 1295-1305 (1984), reported lipoproteins isolated from Golgi were consistently larger than those from the endoplasmic reticulum, again suggesting the assembly of lipoproteins is a progressive event.

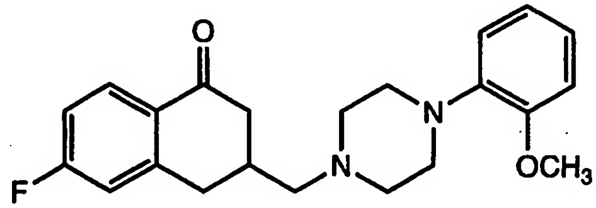
Recent reports (Science, Vol. 258, page 999, 1992; D. Sharp et. al., Nature, Vol. 365, page 65, 1993) demonstrate that the defect causing abetalipoproteinemia is in the MTP gene, and as a result, the MTP protein. Individuals with abetalipoproteinemia have no MTP activity, as a result of mutations in the MTP gene, some of which have been characterized. These results indicate that MTP is required for the synthesis of apoB containing lipoproteins, such as VLDL, the precursor to LDL. It therefore follows that inhibitors of MTP would inhibit the synthesis of VLDL and LDL, thereby lowering VLDL levels, LDL levels, cholesterol levels, and triglyceride levels in animals and man.

Canadian Patent Application No. 2,091,102 published March 2, 1994 (corresponding to U.S. application Serial No. 117,362, filed September 3, 1993 (file DC21b)) reports MTP inhibitors which

also block the production of apoB containing lipoproteins in a human hepatic cell line (HepG2 cells). This provides further support for the proposal that an MTP inhibitor would lower apoB containing lipoprotein and lipid levels in vivo. This Canadian patent application discloses a method for identifying the MTP inhibitors



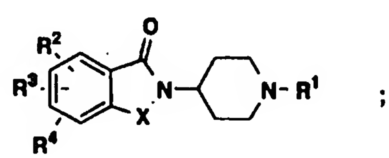
which has the name 2-[1-(3, 3-diphenylpropyl)-4-piperidinyl]-2, 3-dihydro-3-oxo-1H-isoindole hydrochloride and



which has the name 1-[3-(6-fluoro-1-tetralanyl)methyl]-4-O-methoxyphenyl piperazine

EP 0643057A1 published March 15, 1995, discloses MTP inhibitors of the structure

I



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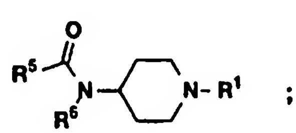

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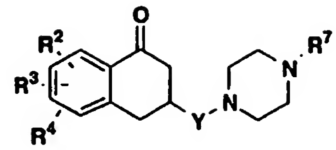


where X is: $CHR^8$, $-\underset{R^9}{\underset{|}{CH}}-\underset{R^{10}}{\underset{|}{CH}}$ or $-\underset{R^9}{\underset{|}{C}}=\underset{R^{10}}{\underset{|}{C}}-$ ;

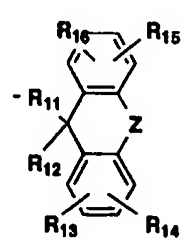
$R^8$, $R^9$ and $R^{10}$ are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

Y is $-(CH_2)_m-$ or $-\overset{}{\underset{O}{\underset{\|}{C}}}-$

where m is 2 or 3;

$R^1$ is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl has at least 2 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl has at least 2 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl has at least 2 carbons); all of the aforementioned $R^1$ groups being optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo; or

$R^1$ is a group of the structure

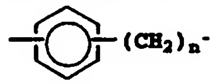


$R^{11}$ is a bond, alkylene, alkenylene or alkynylene of up to 6 carbon atoms, arylene (for example


)

,

or mixed arylene-alkylene (for example



)

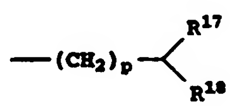
where n is 1 to 6;

$R^{12}$ is hydrogen, alkyl, alkenyl, aryl, heteroaryl, haloalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy, heteroarylalkyl or cycloalkylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

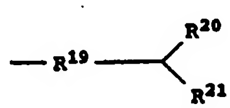
$R^{13}$, $R^{14}$, $R^{15}$, and $R^{16}$ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, carboxy, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or $R^1$ is




wherein p is 1 to 8 and $R^{17}$ and $R^{18}$ are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of $R^{17}$ and $R^{18}$ being other than H;

or $R^1$ is




wherein $R^{19}$ is aryl or heteroaryl;

$R^{20}$ is aryl or heteroaryl;

$R^{21}$ is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

$R^2$, $R^3$, $R^4$ are independently hydrogen, halo, alkyl, haloalkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

$R^5$ is alkyl of at least 2 carbons, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroaryl-alkyl, cycloalkyl, cycloalkylalkyl, polycyclo-alkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl, polycyclo-alkenylalkyl, heteroarylcarbonyl, all of the $R^5$ and $R^6$ substituents being optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkynyl, aryloxy, aryloxyalkyl, aryl-alkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, or aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthio-alkyl, alkylcarbonyl, arylcarbonyl, arylamino-carbonyl, alkoxycarbonyl, aminocarbonyl, alkynyl-aminocarbonyl, alkylaminocarbonyl, alkenylamino-carbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino; with the proviso that when $R^5$ is $CH_3$, $R^6$ is not H; and where $R^5$ is

phenyl, the phenyl preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl, aryl, aryloxy or arylalkyl;

$R^6$ is hydrogen or $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkenyl;

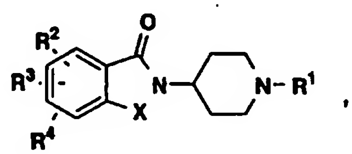
$R^7$ is alkyl, aryl or arylalkyl wherein alkyl or the alkyl portion is optionally substituted with oxo; and

including pharmaceutically acceptable salts and anions thereof.

In the formula I compounds, where X is $CH_2$ and $R^2$ , $R^3$ and $R^4$ are each H, $R^1$ will be other than 3,3-diphenylpropyl.

In the formula III compounds, where one of $R^2$, $R^3$ and $R^4$ is 6-fluoro, and the others are H, $R^7$ will be other than 4-O-methoxyphenyl.

U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e) discloses compounds of the structure



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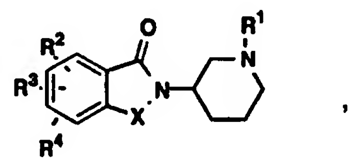

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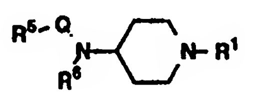

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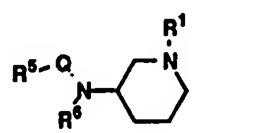

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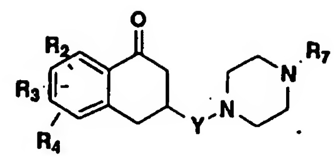


where Q is $-\overset{O}{\overset{\|}{C}}-$ or $-\overset{O}{\overset{\|}{\underset{\underset{O}{\|}}{S}}}-$ ;

X is: $CHR^8$, $-\underset{\underset{O}{\|}}{C}-$ , $-\underset{R^9}{\underset{|}{CH}}-\underset{R^{10}}{\underset{|}{CH}}-$ or $-\underset{R^9}{\underset{|}{C}}=\underset{R^{10}}{\underset{|}{C}}-$ ;

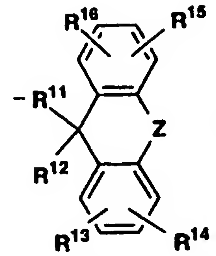
$R^8$, $R^9$ and $R^{10}$ are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

Y is $-(CH_2)_m-$ or $-\underset{\underset{O}{\|}}{C}-$

wherein m is 2 or 3;

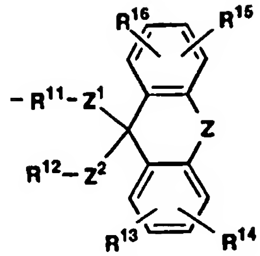
$R^1$ is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl wherein alkyl has at least 2 carbons, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl wherein alkyl has at least 2 carbons, cycloalkyl, or cycloalkylalkyl wherein alkyl has at least 2 carbons, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

or $R^1$ is a fluorenyl-type group of the structure



**A**

or



**B**

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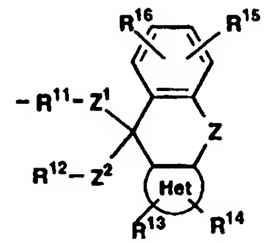
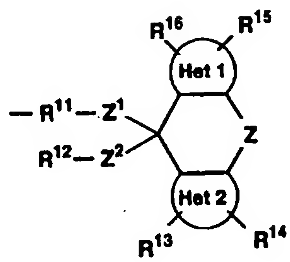


**C**

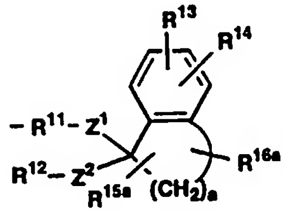
or



**D**

; or

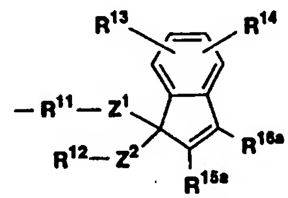
$R^1$ is an indenyl-type group of the structure



**E**

(a = 2,3 or 4)

or



**F**

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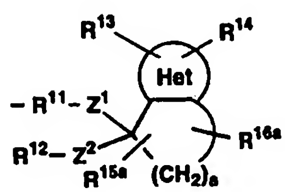

**G**

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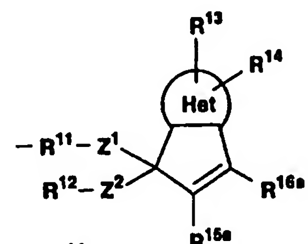


**H**

;

$Z^1$ and $Z^2$ are the same or different and are independently a bond, O, S,

$\underset{\mathrm{O}}{\overset{\|}{\mathrm{S}}}$ , $\underset{(\mathrm{O})_2}{\overset{\|}{\mathrm{S}}}$ , $-\mathrm{NH}-\underset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-$ , $-\underset{\text{alkyl}}{\mathrm{N}}-\underset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-$ , $-\underset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-$ or $-\underset{\mathrm{OH}}{\overset{\mathrm{H}}{\mathrm{C}}}-$ ,

with the proviso that with respect to B, at least one of $Z^1$ and $Z^2$ will be other than a bond; $R^{11}$ is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; $R^{12}$ is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

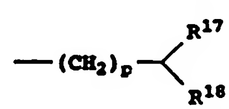
(1) when $R^{12}$ is H, aryloxy, alkoxy or arylalkoxy, then $Z^2$ is $-NH-\overset{\displaystyle O}{\overset{\|}{C}}-$ , $-\underset{\text{alkyl}}{\underset{|}{N}}-\overset{\displaystyle O}{\overset{\|}{C}}-$ , $-\overset{\displaystyle O}{\overset{\|}{C}}-$ or a bond and

(2) when $Z^2$ is a bond, $R^{12}$ cannot be heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; $R^{13}$, $R^{14}$, $R^{15}$, and $R^{16}$ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

$R^{15a}$ and $R^{16a}$ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

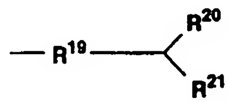
or $R^1$ is a group of the structure



wherein p is 1 to 8 and $R^{17}$ and $R^{18}$ are each independently H, alkyl, alkenyl, aryl, arylalkyl,

heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of $R^{17}$ and $R^{18}$ being other than H;

or $R^1$ is a group of the structure



wherein $R^{19}$ is aryl or heteroaryl;

$R^{20}$ is aryl or heteroaryl;

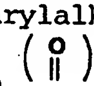
$R^{21}$ is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

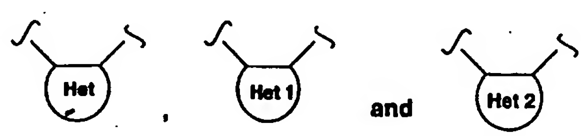
$R^2$, $R^3$, $R^4$ are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

$R^5$ is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cyclohetero-alkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cyclohetero-alkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino,

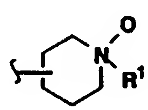
thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl;

$R^6$ is hydrogen or $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkenyl; all optionally substituted with 1, 2, 3 or 4 groups which may independently be any of the substituents listed in the definition of $R^5$ set out above;

$R^7$ is alkyl, aryl or arylalkyl wherein alkyl by itself or as part of arylalkyl is optionally substituted with oxo ;



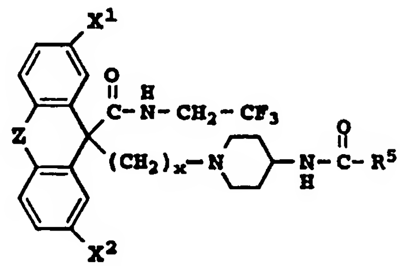
are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

N-oxides  thereof; and

pharmaceutically acceptable salts thereof;

with the provisos that where in the first formula X is $CH_2$, and $R^2$, $R^3$ and $R^4$ are each H, then $R^1$ will be other than 3,3-diphenylpropyl, and in the fifth formula, where one of $R^2$, $R^3$ and $R^4$ is 6-fluoro, and the others are H, $R^7$ will be other than 4-(2-methoxyphenyl).

U.S. application Serial No. 548,811 filed January 11, 1996 (file DC21h), discloses compounds having the structure



including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof, wherein Z is a bond, O or S;

$X^1$ and $X^2$ are independently selected from H or halo;

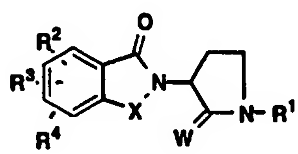
x is an integer from 2 to 6;

$R^5$ is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each $R^5$ group being optionally substituted with 1, 2, 3 or 4 substituents which may be the same or different.

## Summary of the Invention

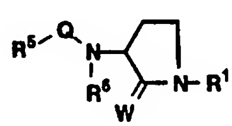
In accordance with the present invention, novel compounds are provided which are inhibitors of MTP and have the structure

I

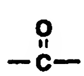
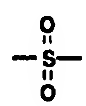


; or

II



;

where Q is  or  ;

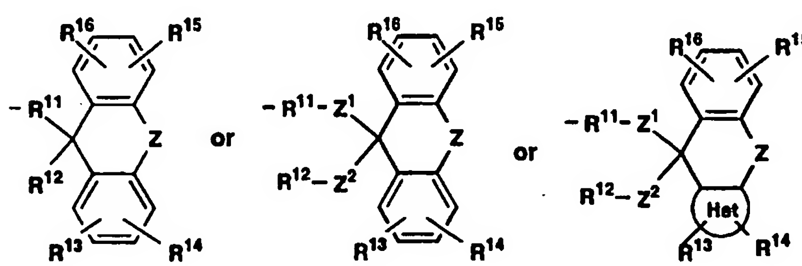
W is H,H or O;

X is: $CHR^8$, $-C(=O)-$, $-CH(R^9)-CH(R^{10})-$ or $-C(R^9)=C(R^{10})-$;

$R^8$, $R^9$ and $R^{10}$ are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

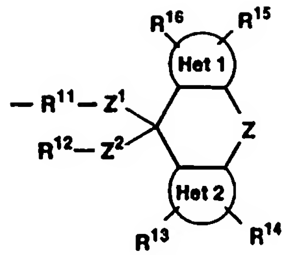
$R^1$ is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons); all of the aforementioned $R^1$ groups being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo; or

$R^1$ is a fluorenyl-type group of the structure



A B C

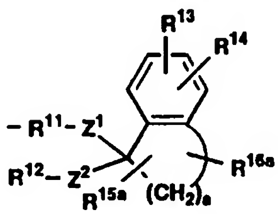
or



; or

D

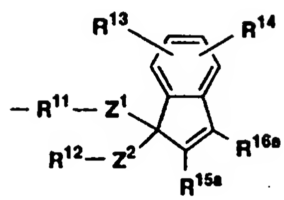
$R^1$ is an indenyl-type group of the structure



E

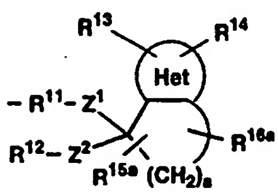
(a = 2,3 or 4)

or



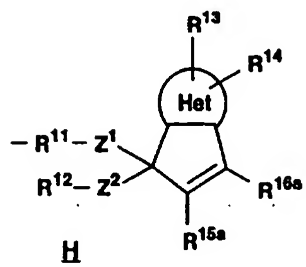
F

or



G

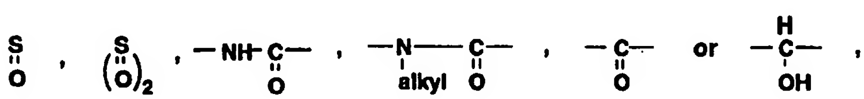
or



H

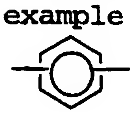
;

$Z^1$ and $Z^2$ are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of $Z^1$ and $Z^2$ will be other than a bond;

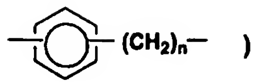
$R^{11}$ is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example



)

,

or mixed arylene-alkylene (for example



where n is 1 to 6;

$R^{12}$ is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the provisos that (1) when $R^{12}$ is H, aryloxy, alkoxy or arylalkoxy, then $Z^2$ is $-NH-\overset{O}{\overset{\|}{C}}-$, $-\underset{alkyl}{N}-\overset{O}{\overset{\|}{C}}-$, $-\overset{O}{\overset{\|}{C}}-$ or a bond;

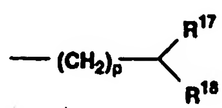
and (2) when $Z^2$ is a bond, $R^{12}$ cannot be heteroaryl or heteroarylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

$R^{13}$, $R^{14}$, $R^{15}$, and $R^{16}$ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

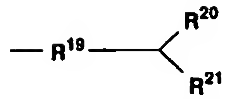
$R^{15a}$ and $R^{16a}$ are independently any of the $R^{15}$ or $R^{16}$ groups except hydroxy, nitro, amino or thio;

or $R^1$ is



wherein p is 1 to 8 and $R^{17}$ and $R^{18}$ are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of $R^{17}$ and $R^{18}$ being other than H;

or $R^1$ is



wherein $R^{19}$ is aryl or heteroaryl;

$R^{20}$ is aryl or heteroaryl;

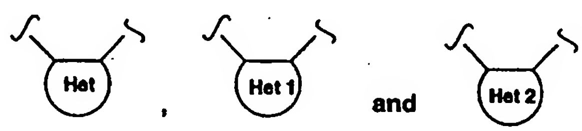
$R^{21}$ is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

$R^2$, $R^3$, $R^4$ are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

$R^5$ is alkyl , alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloheteroalkyl, heteroaryloxy, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all of the $R^5$ substituents and $R^6$ substituents (set out hereinafter) being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, aryl or heteroaryl, or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio,

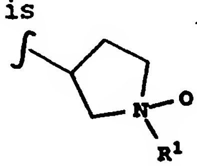
heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylamino-carbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonyl-amino, arylsulfinyl, arylsulfinylalkyl, aryl-sulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl. Where $R^5$ is phenyl, aryl, heteroaryl or cycloalkyl; this group preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl (with up to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo groups), aryl, aryloxy or arylalkyl;

$R^6$ is hydrogen or $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkenyl;




are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

including N-oxides of the formulae I and II compounds, that is



; and

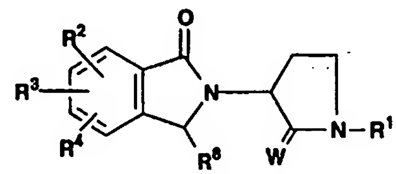
including pharmaceutically acceptable salts thereof such as alkali metal salts such as lithium sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butyl-amine, t-octylamine, dehydroabietylamine, as well as pharmaceutically acceptable anions such as

chloride, bromide, iodide, tartrate, acetate, methanesulfonate, maleate, succinate, glutarate, and salts of naturally occurring amino acids such as arginine, lysine, alanine and the like, and prodrug esters thereof.

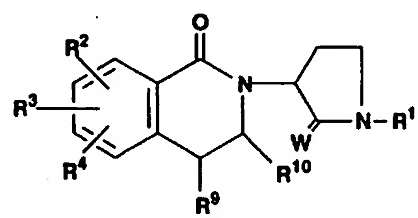
In the formula I compounds, where X is $CH_2$ and $R^2$ , $R^3$ and $R^4$ are each H, $R^1$ will preferably be other than 3,3-diphenylpropyl.

Thus, the compounds of formulae I and II of the invention encompass compounds of the structure

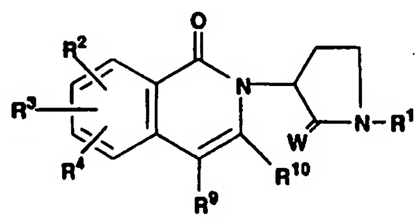
$I^a$



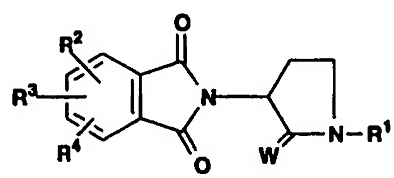
$I^b$



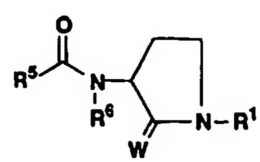
$I^c$



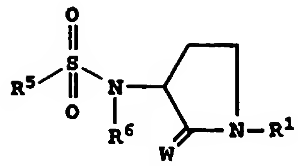
$I^d$



$II^a$



IIb



It will be understood that the pyrrolidinyl ring shown in the above formulas depicting compounds of the invention as well as in starting materials and intermediates shown in the Reaction Schemes to follow can be in racemic form or are R- or S-enantiomers.

In addition, in accordance with the present invention, a method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity is provided, wherein a compound of formula I or II as defined hereinbefore is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

Furthermore, in accordance with the present invention, a method is provided for lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, wherein a compound of formula I or II is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

## Detailed Description of the Invention

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "MTP" refers to a polypeptide or protein complex that (1) if obtained from an organism (e. g., cows, humans, etc.), can be isolated from the microsomal fraction of homogenized tissue; and (2) stimulates the transport of triglycerides, cholesterol esters, or

phospholipids from synthetic phospholipid vesicles, membranes or lipoproteins to synthetic vesicles, membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein [Drayna et al., Nature 327, 632-634 (1987)] which may have similar catalytic properties. However, the MTP molecules of the present invention do not necessarily need to be catalytically active. For example, catalytically inactive MTP or fragments thereof may be useful in raising antibodies to the protein.

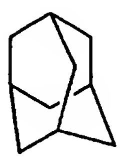
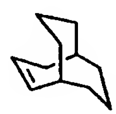
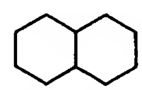
The phrase "stabilizing" atherosclerosis as used in the present application refers to slowing down the development of and/or inhibiting the formation of new atherosclerotic lesions.

The phrase "causing the regression of" atherosclerosis as used in the present application refers to reducing and/or eliminating atherosclerotic lesions.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 12 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or $CF_3$, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl,

aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio, as well as any of the other substituents as defined for $R^5$ and $R^6$.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,

 ,  ,  ,  ,

any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for $R^5$ or $R^6$.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 5 to 20 carbons, preferably 6 to 12 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "polycycloalkyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20 carbons and containing 0 to 3 bridges, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclo-octanyl, adamantanyl, [2.2.1]-bicycloheptanyl, [2.2.2]-bicyclooctanyl and the like and may be optionally substituted as defined for cycloalkyl.

The term "polycycloalkenyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20 carbons and containing 0 to 3 bridges and containing 1 or 2 double bonds, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycyclo-alkyl groups include [3.3.0]-bicyclooctenyl, [2.2.1]-bicycloheptenyl, [2.2.2]-bicyclooctenyl and the like and may be optionally substituted as defined for cycloalkyl.

The term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to Ar (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoro-methyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxy-alkyl, arylalkoxy, arylthio, arylazo, hetero-arylalkyl, heteroarylalkenyl, heteroarylhetero-aryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or

2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl, or any of the substituents as defined for the $R^5$ or $R^6$ groups set out above.

The term "aralkyl", "aryl-alkyl" or "aryllower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl substituent, such as benzyl or phenethyl, or naphthylpropyl, or an aryl as defined above.

The term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "amino" as employed herein alone or as part of another group may optionally be substituted with one or two substituents such as alkyl and/or aryl.

The term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "acyl" as employed herein by itself or part of another group as defined herein, refers to an organic radical linked to a carbonyl ($\overset{O}{\overset{\|}{C}}$) group, examples of acyl groups include alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl and the like.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 3 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents; namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for $R^5$ or $R^6$.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-

pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, as well as any of the other substituents as defined for $R^5$ or $R^6$.

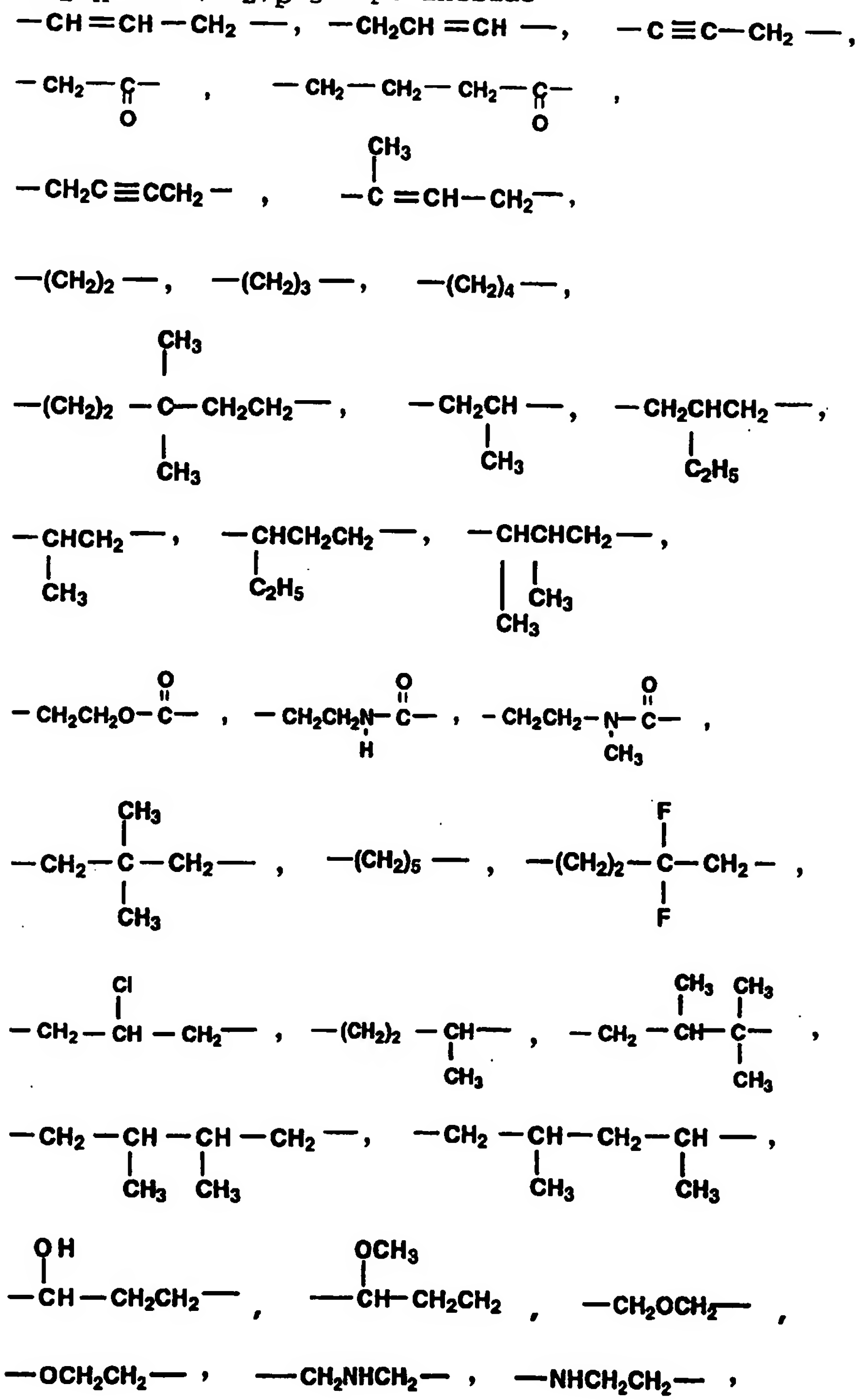
The term "alkylene" as employed herein alone or as part of another group (which also encompasses "alkyl" as part of another group such as arylalkyl or heteroarylalkyl) refers to alkyl groups as defined above having single bonds for attachment to other groups at two different carbon atoms and may optionally be substituted as defined above for "alkyl". The definition of alkylene applies to an alkyl group which links one function to another, such as an arylalkyl substituent.

The terms "alkenylene" and "alkynylene" as employed herein alone or as part of another group (which also encompass "alkenyl" or "alkynyl" as part of another group such as arylalkenyl or arylalkynyl), refer to alkenyl groups as defined above and alkynyl groups as defined above, respectively, having single bonds for attachment at two different carbon atoms.

Suitable alkylene, alkenylene or alkynylene groups or $(CH_2)_n$ or $(CH_2)_p$ (which may include alkylene, alkenylene or alkynylene groups) as defined herein, may optionally include 1,2, or 3 alkyl, alkoxy, aryl, heteroaryl, cycloheteroalkyl, alkenyl, alkynyl, oxo, aryloxy, hydroxy, halogen substituents as well as any of the substituents defined for $R^5$ or $R^6$, and in addition, may have one

of the carbon atoms in the chain replaced with an oxygen atom, N-H, N-alkyl or N-aryl.

Examples of alkylene, alkenylene, alkynylene, $(CH_2)_n$ and $(CH_2)_p$ groups include



$$-(CH_2)_3-CF_2- \;,\quad -CH_2-\overset{CH_3}{\overset{|}{N}}-CH_2- \;,\quad -\underset{CH_3}{\underset{|}{N}}-CH_2CH_2- \;,$$

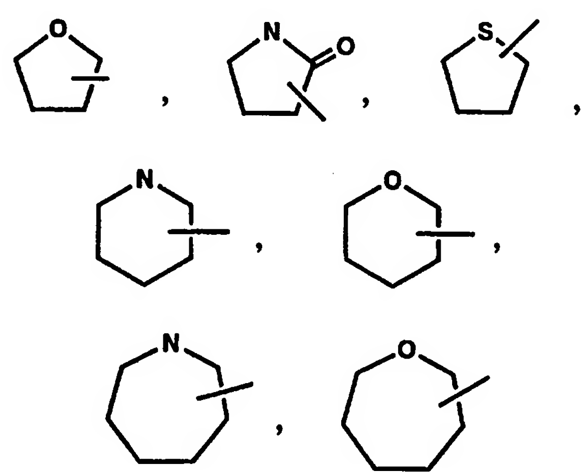
$$-(CH_2)_2-\overset{F}{\overset{|}{\underset{H}{\underset{|}{C}}}}-CH_2- \;,\quad -(CH_2)_2-\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-CH_2- \;,$$

$$-(CH_2)_2-\overset{CH_3}{\overset{|}{\underset{H}{\underset{|}{C}}}}-CH_2- \;,\quad -(CH_2)_3-\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}- \quad \text{or} \quad -(CH_2)_3-\overset{CH_3}{\overset{|}{\underset{H}{\underset{|}{C}}}}- .$$

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as $CF_3$, with chlorine or fluorine being preferred.

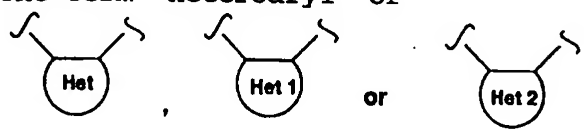
The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

The term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as

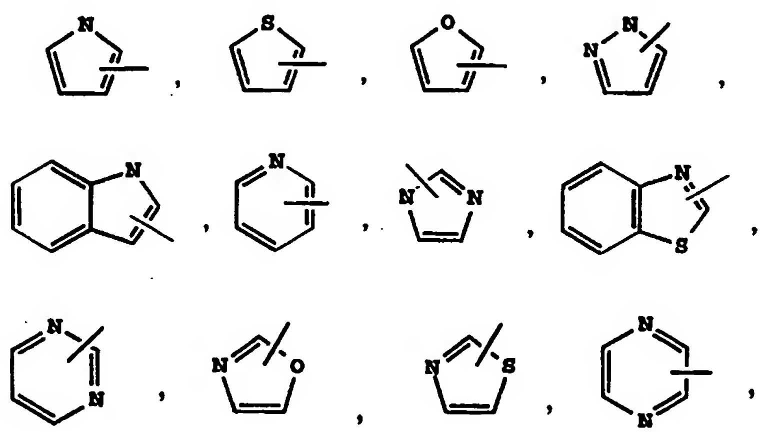


and the like. The above groups may include 1 to 3 substituents such as any of the $R^1$, $R^5$ or $R^6$ groups as defined above. In addition, any of the above rings can be fused to 1 or 2 cycloalkyl, aryl, heteroaryl or cycloheteroalkyl rings.

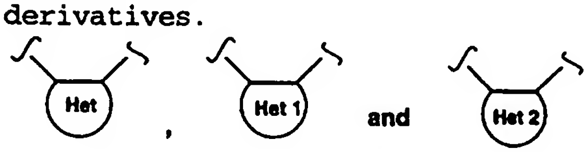
The term "heteroaryl" or




(also referred to as heteroaryl) as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as

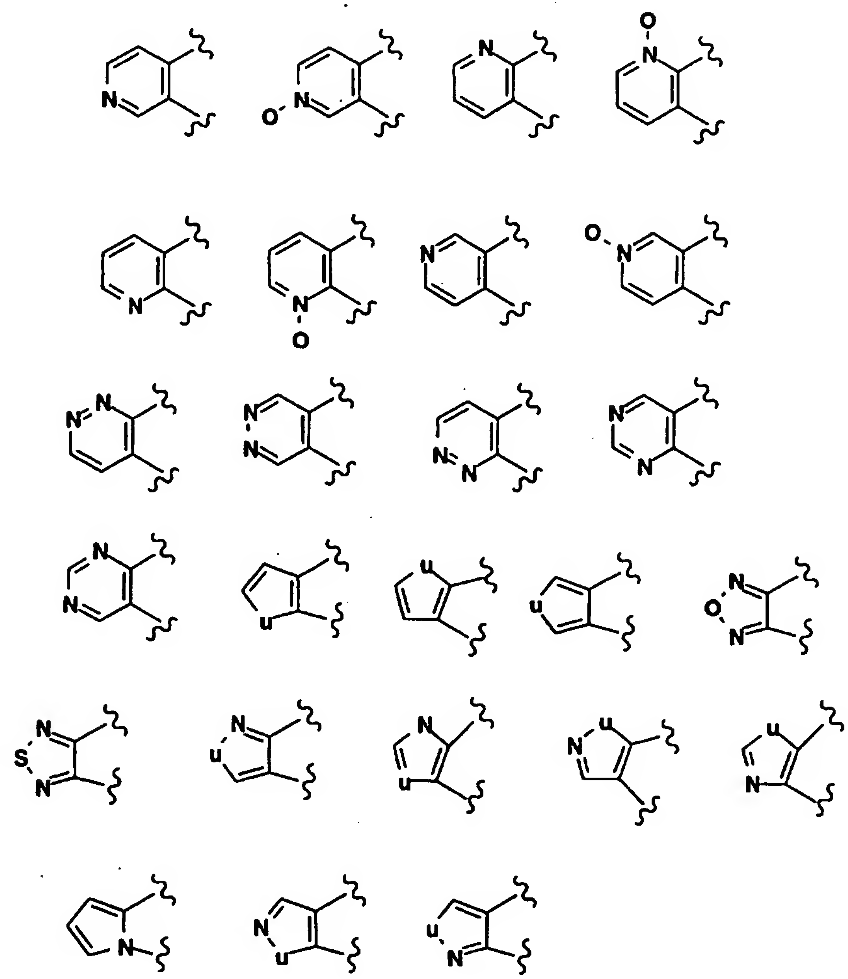


and the like, and includes all possible N-oxide derivatives.




are the same or different as defined hereinbefore and are attached to the central ring of the indenyl or fluorenyl type group at adjacent

positions (that is ortho or 1,2-positions). Examples of such groups include



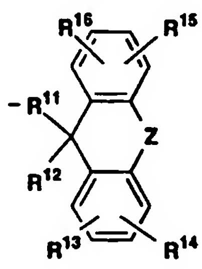
wherein u is selected from O, S, and $NR^{7a}$; $R^{7a}$ is H, lower alkyl, aryl, $-C(O)R^{7b}$, $-C(O)OR^{7b}$; $R^{7b}$ is alkyl or aryl, and includes all possible N-oxide derivatives.

The heteroaryl groups including the above groups may optionally include 1 to 4 substituents such as any of the substituents listed for aryl, or those substituents indicated for $R^5$ or $R^6$ groups as defined above. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

The term cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_p$ chain.

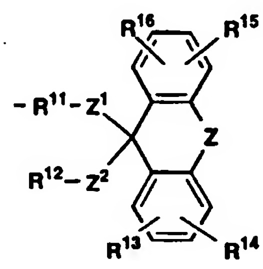
The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_p-$ chain, alkylene or alkenylene as defined above.

The term "fluorenyl" or "fluorenyl analog" or "fluorenyl-type group" as employed herein refers to a group of the structure:



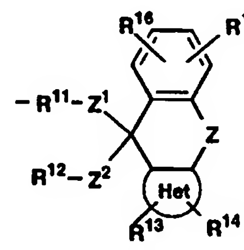
A

or



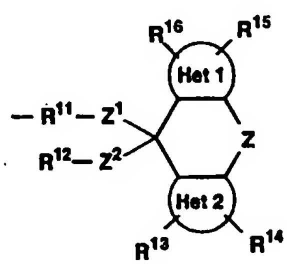
B

or



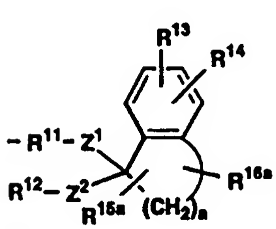
C

or



D

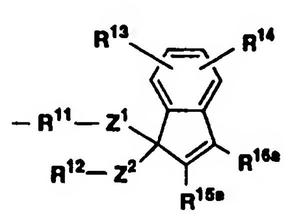
The term "indenyl-type group" as employed herein refers to a group of the structure



E

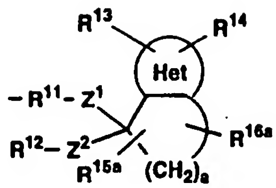
(a = 2,3 or 4)

or



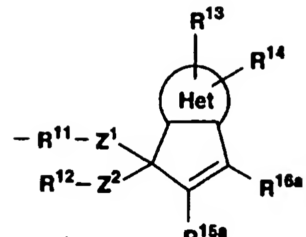
E

or



G

or



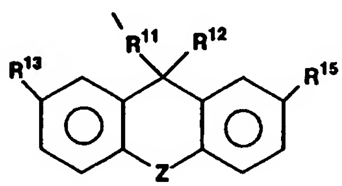
H

;

Z, $Z^1$, $Z^2$, $R^{11}$, $R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$, $R^{16}$, $R^{15a}$ and $R^{16a}$ as used in the above groups A through H are as defined hereinbefore.

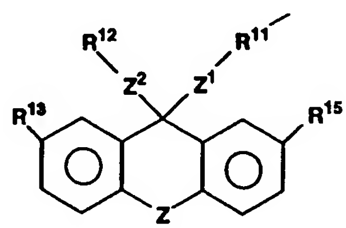
Preferred are compounds of formulae I and II wherein

$R^1$ is arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl,

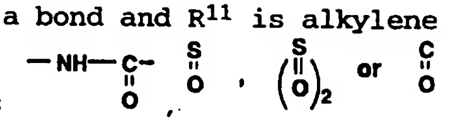


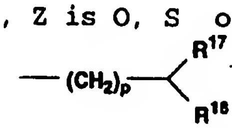
A'

or

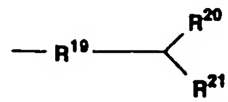


B'

(including where $Z^1$ is a bond and $R^{11}$ is alkylene or alkenylene and $Z^2$ is  and $R^{12}$ is $C_1$-$C_3$ alkyl or 1,1,1-trifluoroethyl, $R^{13}$ is H or F and $R^{15}$ is H or F, and Z is a bond or O; and where $R^{11}$ is alkylene or alkenylene or alkylene substituted with oxo, $R^{12}$ is alkyl, alkenyl, aralkyl, aralkenyl, Z is O, S or a bond); or



(wherein $R^{17}$ and $R^{18}$ are each independently alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl); or



wherein $R^{19}$ is aryl or heteroaryl;

$R^{20}$ is aryl or heteroaryl;

$R^{21}$ is alkyl, aryl, alkylaryl, arylalkyl aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy.

In structure I, it is preferred that $R^2$, $R^3$ and $R^4$ are each H and X is $CH_2$, $CH_2CH_2$, or CH=CH.

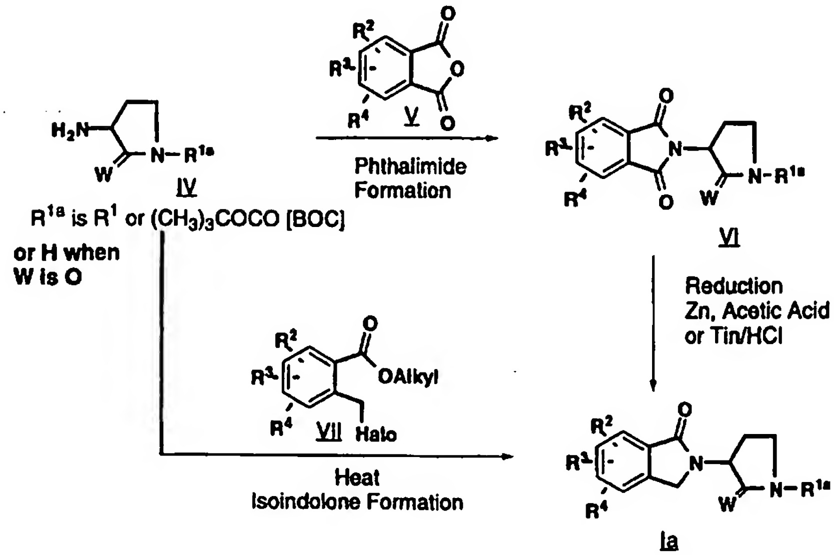
In structure II, it is preferred that $R^6$ is H or $CH_3$ and $R^5$ is cycloalkyl, phenyl, aryl or heteroaryl, or cycloalkyl, phenyl, aryl heteroaryl having an ortho hydrophobic substituent which is alkyl, alkoxy, haloalkyl (containing up to five halo groups), trifluoromethyl, aryl, aryloxy, arylalkyl, arylalkoxy, haloalkoxy (containing up to five halo groups).

In structure II, it is also preferred that $R^1$ is arylalkyl or heteroarylalkyl wherein alkyl of each has at least 2 carbons (preferably at least 3 carbons) and $R^5$ and $R^6$ may be as defined hereinbefore and may or may not be the preferred groups set out above.

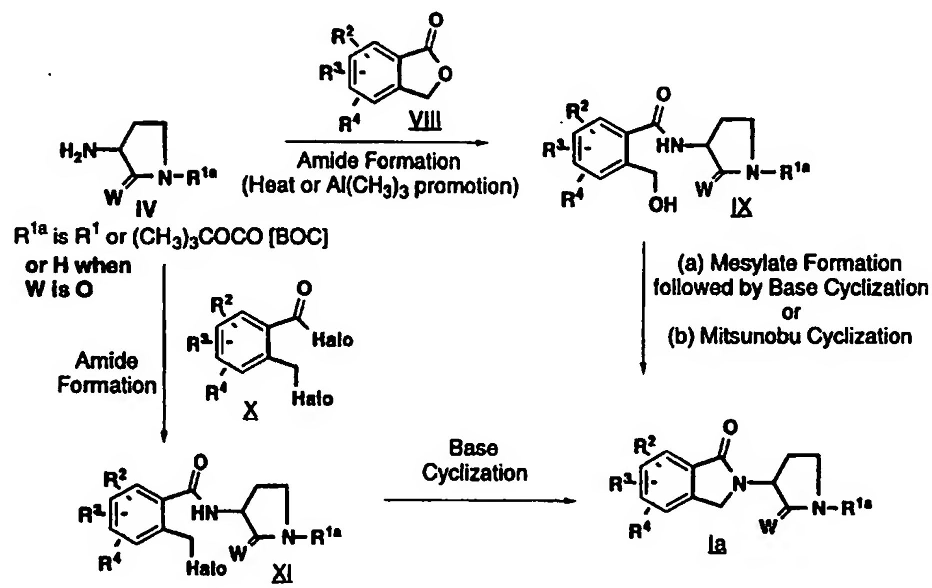
It is to be understood that combinations of substituents which lead to chemically unstable molecules are not included within the scope of the present invention; for example, compounds of the invention will not include -O-O-, -O-C-OH, N-C-OH and -S-C-OH linkages.

The compounds of formulae I and II may be prepared by the exemplary processes described in the following reaction schemes. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

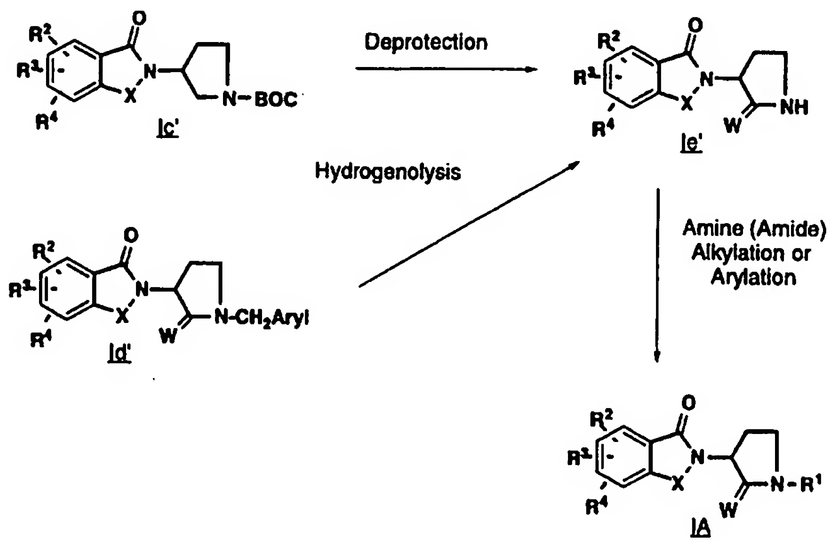
Scheme I. Routes to Isoindolinone Piperidines



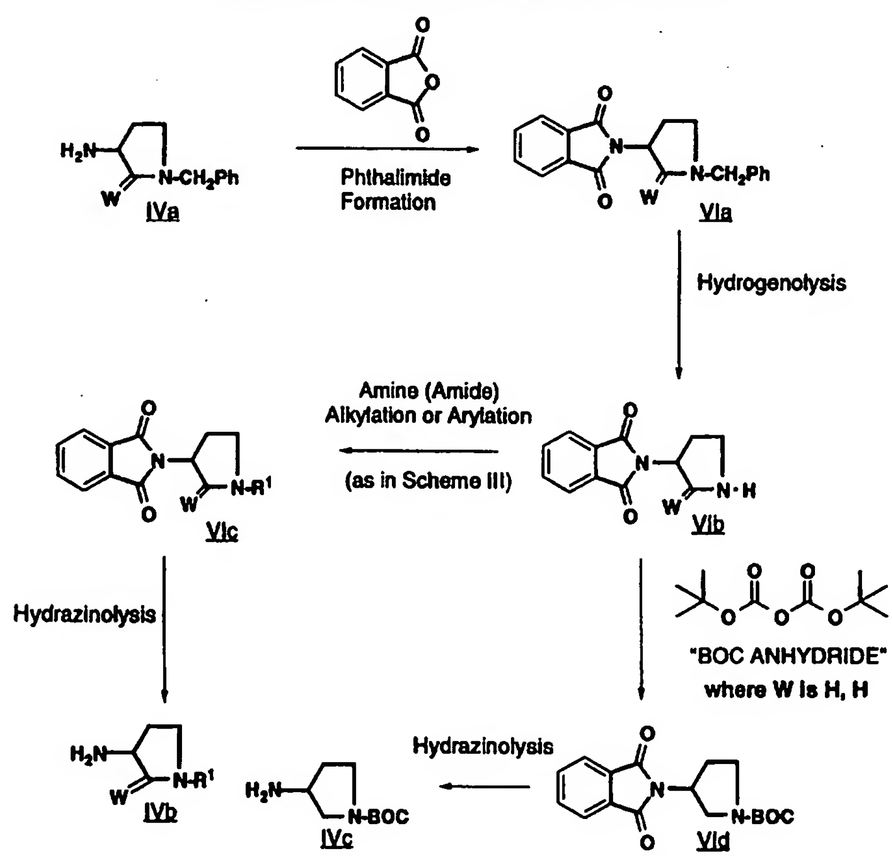

Scheme II. Additional Routes to Isoindolinone Piperidines



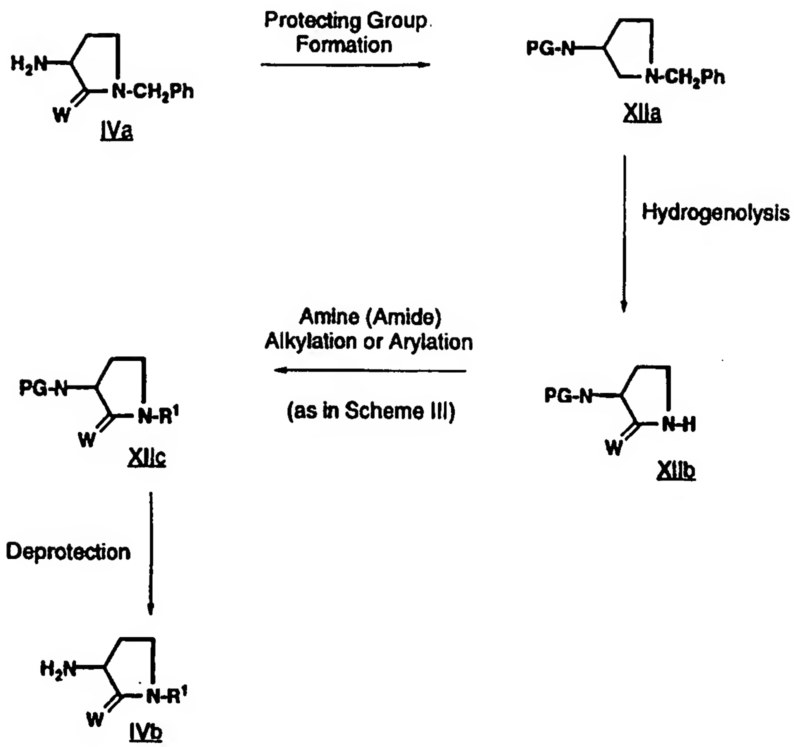
Scheme III. Introduction of $R^1$ by Alkylation or Arylation



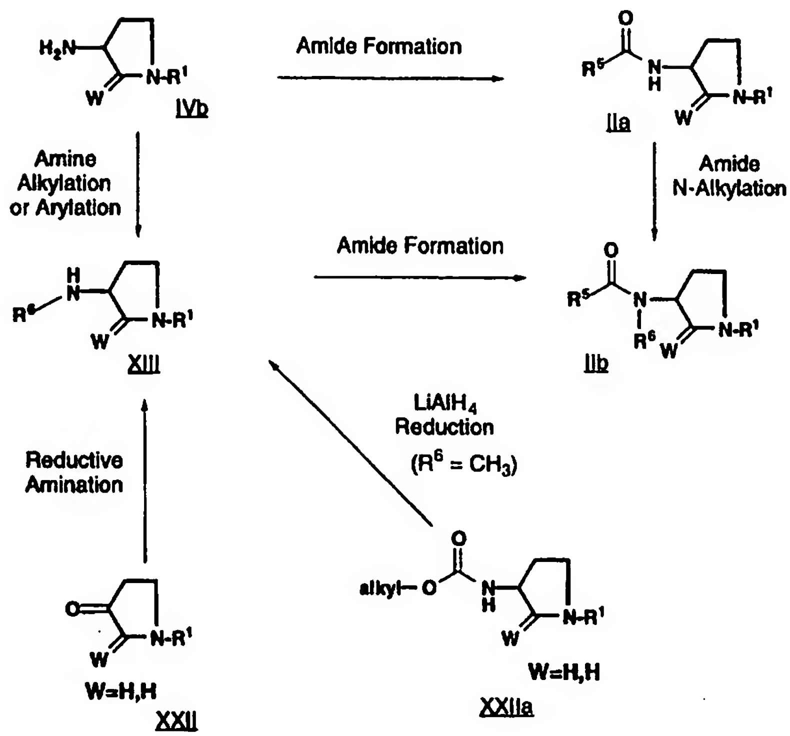

Scheme IV. Routes to Starting Materials IVb and IVc



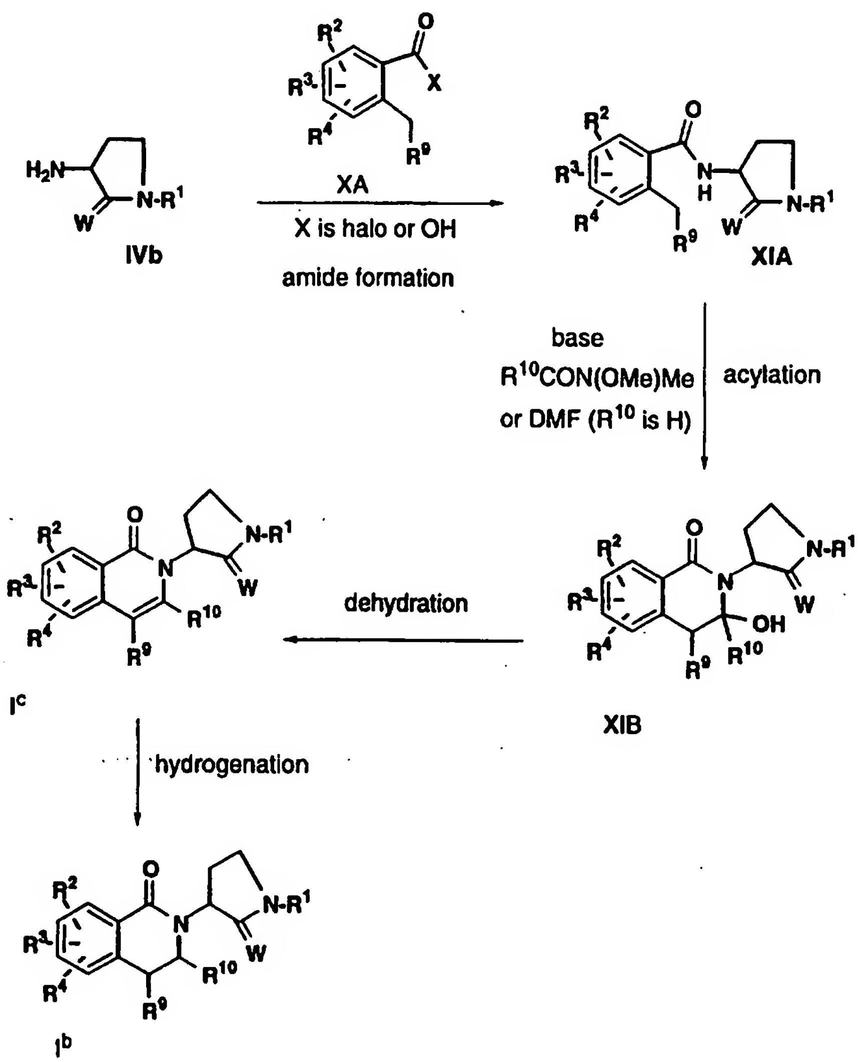
Scheme V. General Routes to Starting Materials IVb



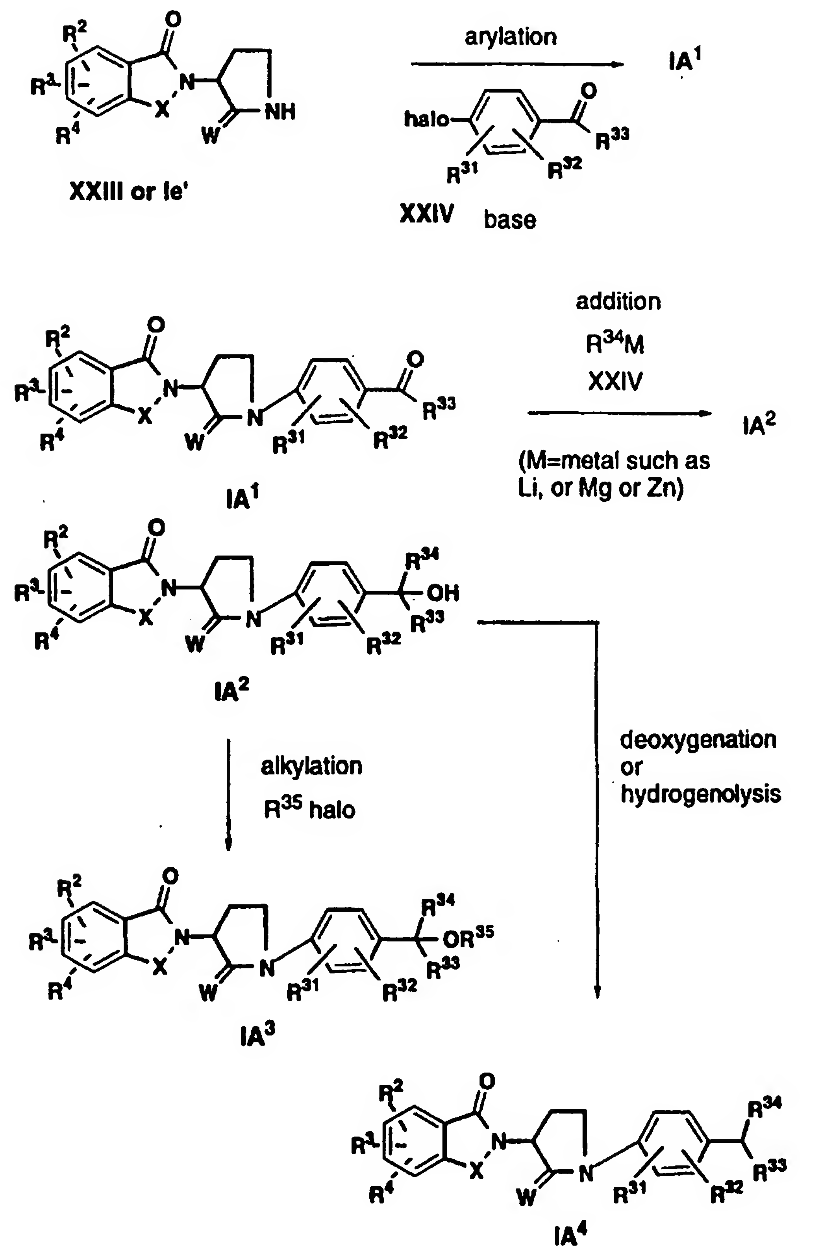
Schemes VI and VII. General Routes to II



Scheme VIII Preparation of Compounds $I^b$, $I^c$



Scheme IX Preparation of Compounds $IA^1$-$IA^2$

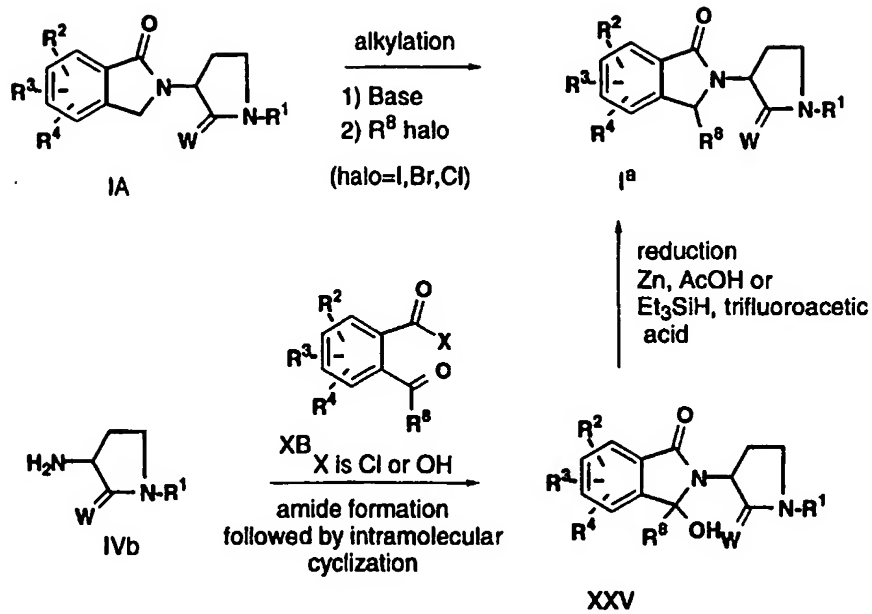



$R^{31}$ and $R^{32}$ are independently selected from any of the $R^2$, $R^3$, or $R^4$ radicals;

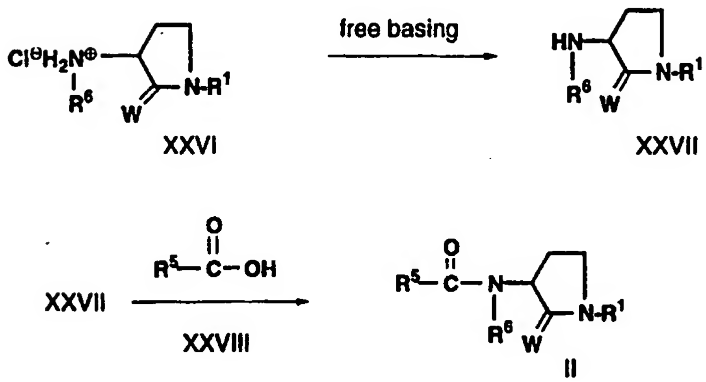
$R^{33}$ and $R^{34}$ are independently selected from any of the $R^1$ radicals as well as aryloxy, alkoxy, arylalkoxy, heteroarylalkoxy and heteroaryloxy;

$R^{35}$ can be any of the $R^1$ radicals.

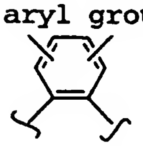
Scheme X Preparation of Compound I[a]




Scheme XI Preparation of Compound II
(Robotic Amide Coupling)

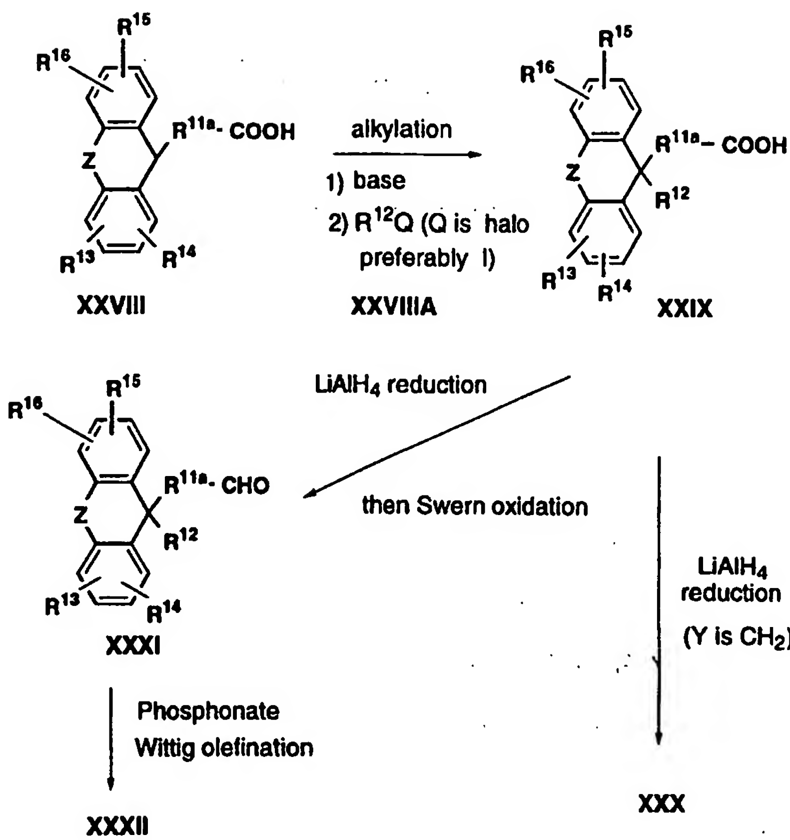



In the following Schemes XII et al, in the fluorenyl rings or fluorenyl analogs, the fused aryl groups:

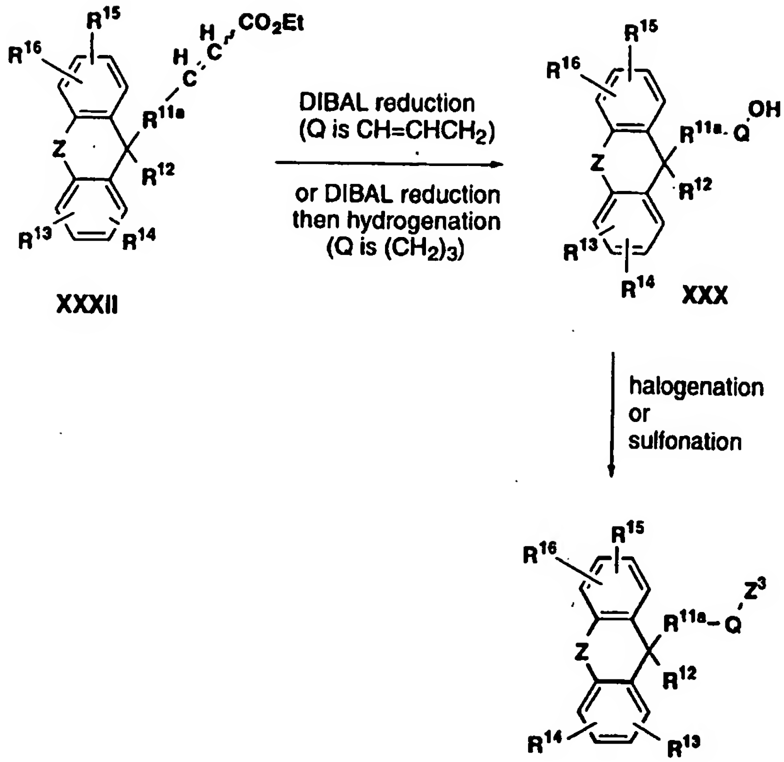


may each optionally be replaced by a 5- or 6-membered heteroaryl ring as defined herein.

Scheme XII




$R^{11a}$ can be any of the $R^{11}$ radicals.



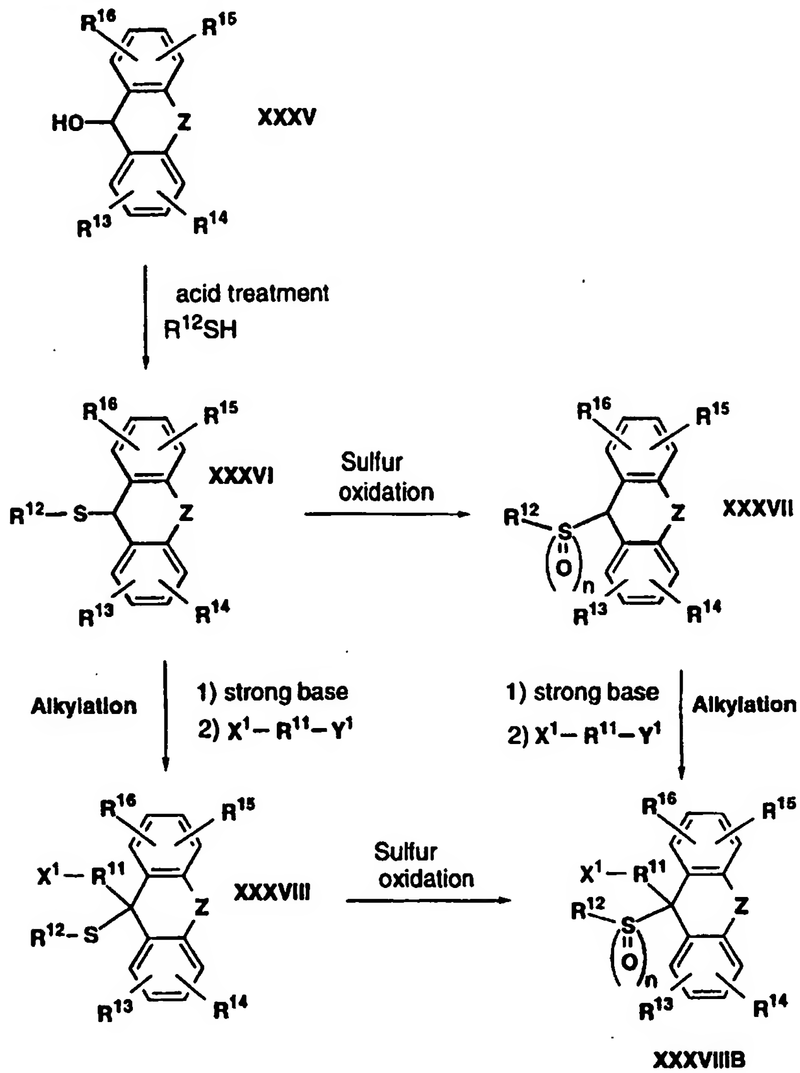

XXXII

XXX

XXXIIIA

$Z^3$ is halo or Osulfonate

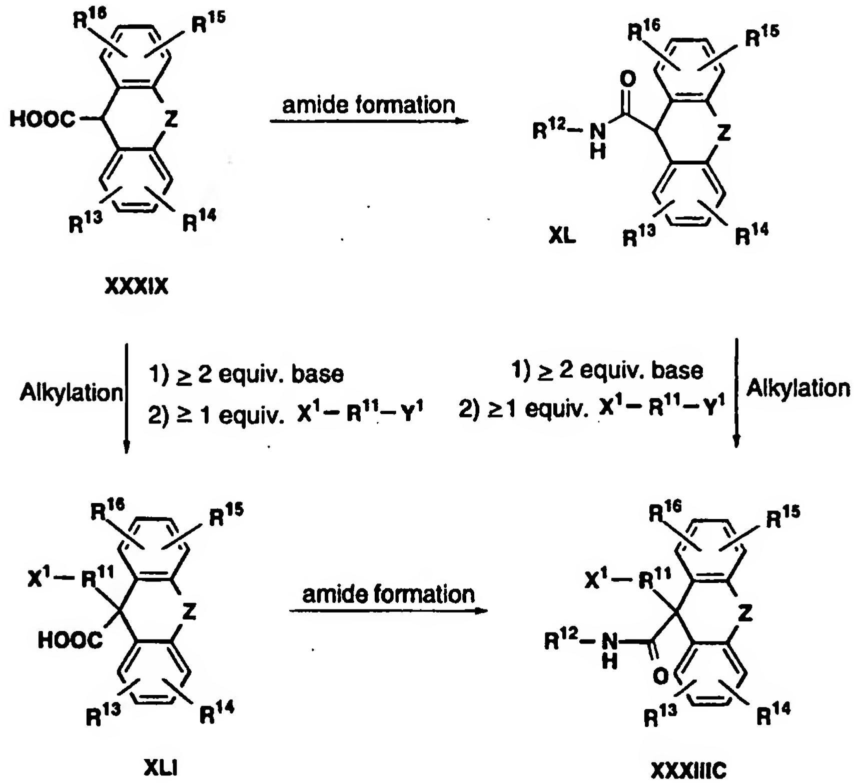
Scheme XIII - Preparation of Intermediates where $Z^2$ is S, SO or $SO_2$




$X^1$, $Y^1$ are same or different halo or Osulfonate

n = 1 or 2

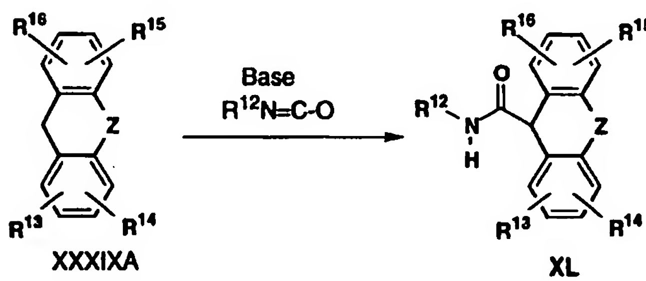
Scheme XIVA - Preparation of A (Intermediates where $Z^2$ is NHCO)




$X^1$, $Y^1$ are same or different halo or Osulfonate

Scheme XIVB

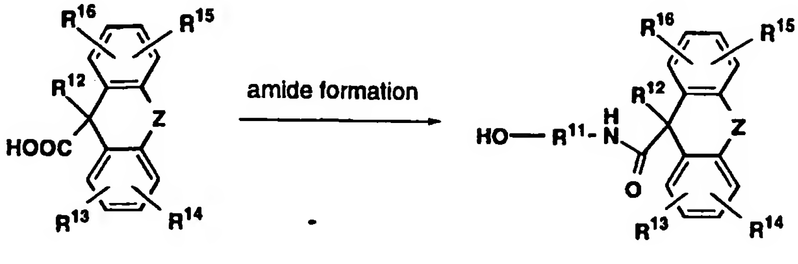
Alternative Procedure for Preparing Intermediate XL (Shown in Scheme XIVA)



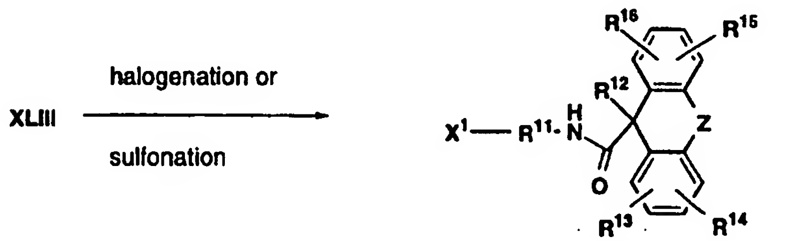

In carrying out the above reaction, bases such as n-butyllithiun, lithium bis(trimethylsilyl) amide and sodium bis(trimethylsilyl) amide may be employed in an aprotic solvent such as THF, at between -78°C and 35°C.

It is preferable to have the starting material and isocyanate ($R^{12}N{=}C{-}O$) together in solvent, and then add the base, and optionally add further excess isocyanate subsequently.

<u>Scheme XV</u> - Preparation of Intermediate where $Z^1$ is $-\overset{H}{N}-\underset{O}{\overset{\|}{C}}-$



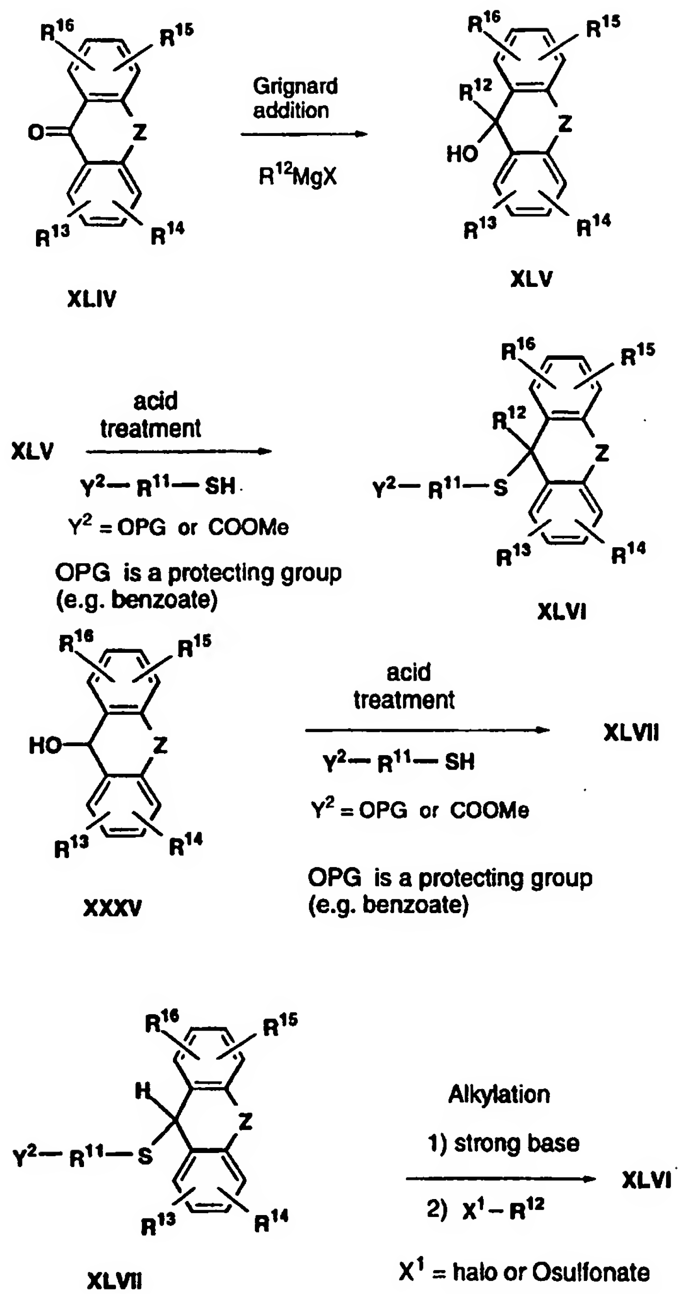

XLII XLIII

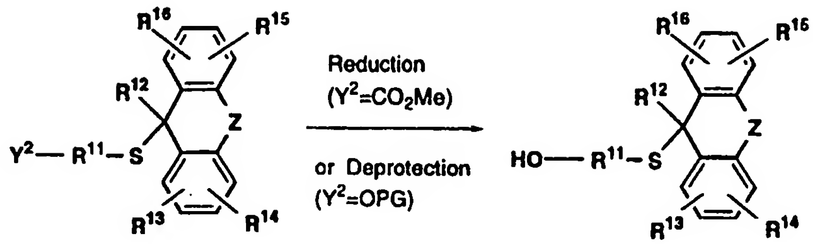



XXXIIID

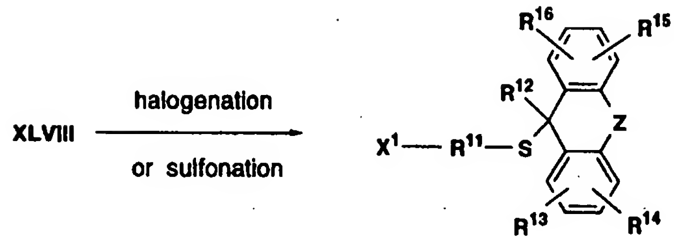
$X^1$ is halo or Osulfonate

Scheme XVI


Grignard addition
$R^{12}MgX$
XLIV
XLV
acid treatment
$Y^2—R^{11}—SH$
$Y^2$ = OPG or COOMe
OPG is a protecting group (e.g. benzoate)
XLVI
XXXV
XLVII
Alkylation
1) strong base
2) $X^1-R^{12}$
$X^1$ = halo or Osulfonate

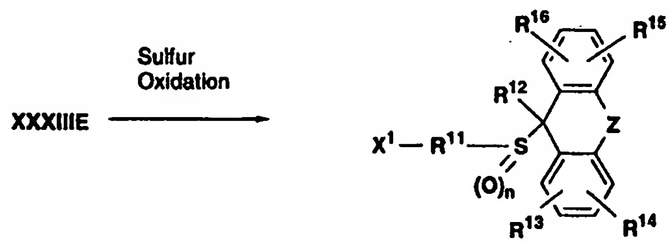


XLVI XLVIII



$X^1$ is halo or Osulfonate

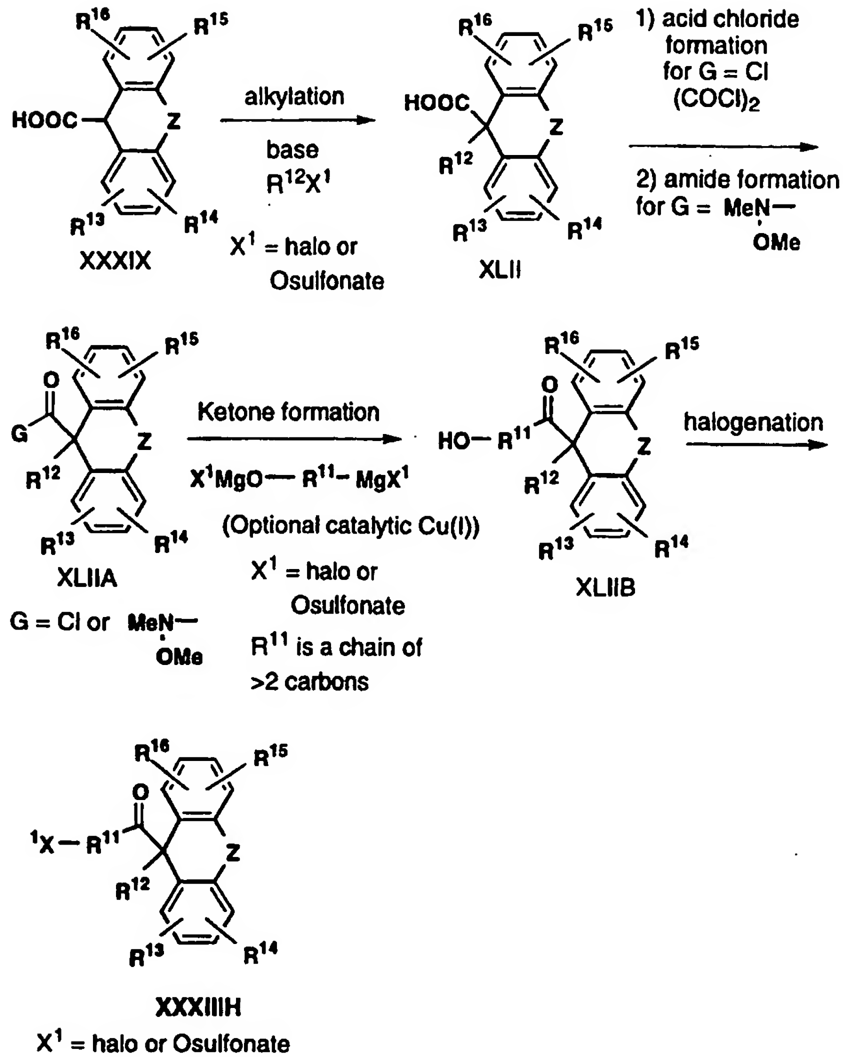
XXXIIIE



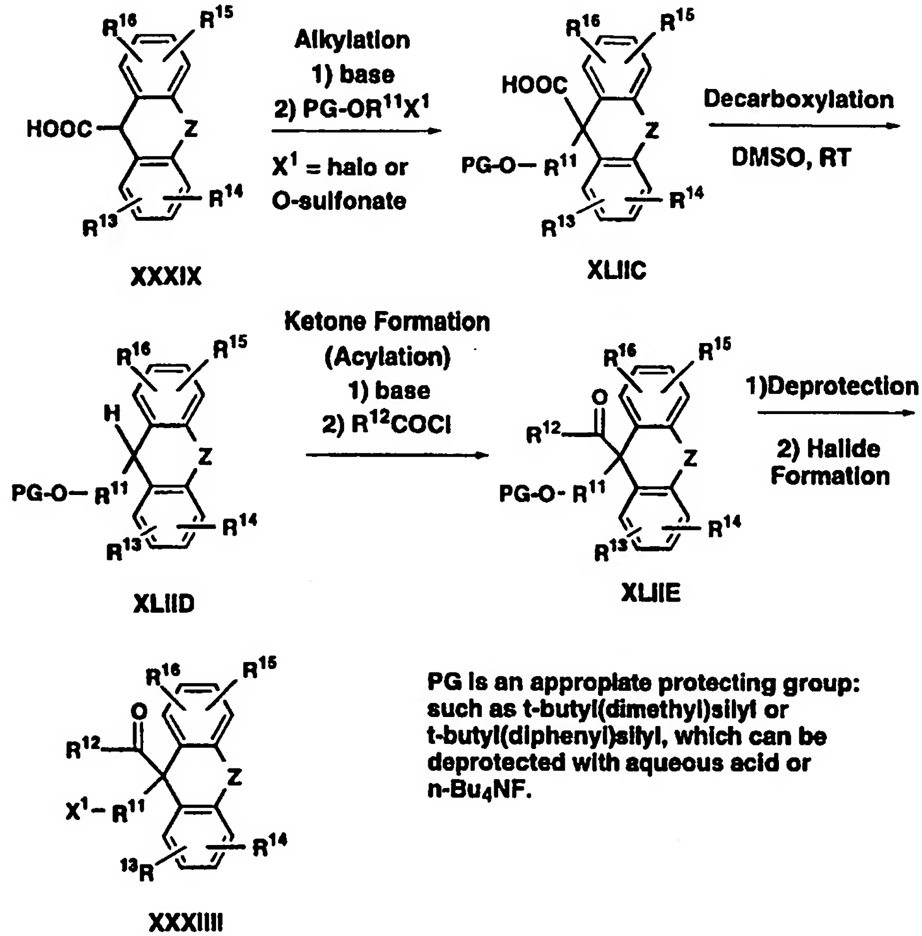
XXXIIIF (n=1)

XXXIIIG (n=2)

Scheme XVIA Preparation of Ketones

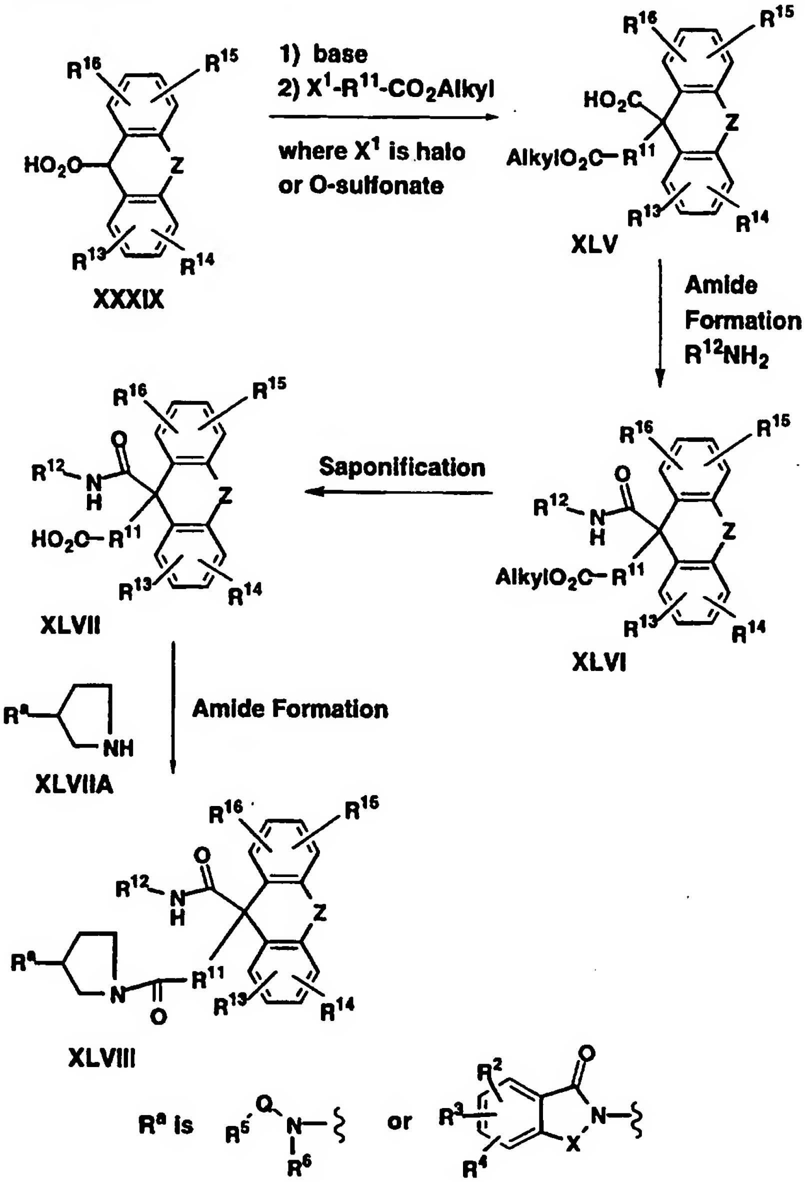


**Scheme XVIB. Preparation of Ketones (Preferred Route)**

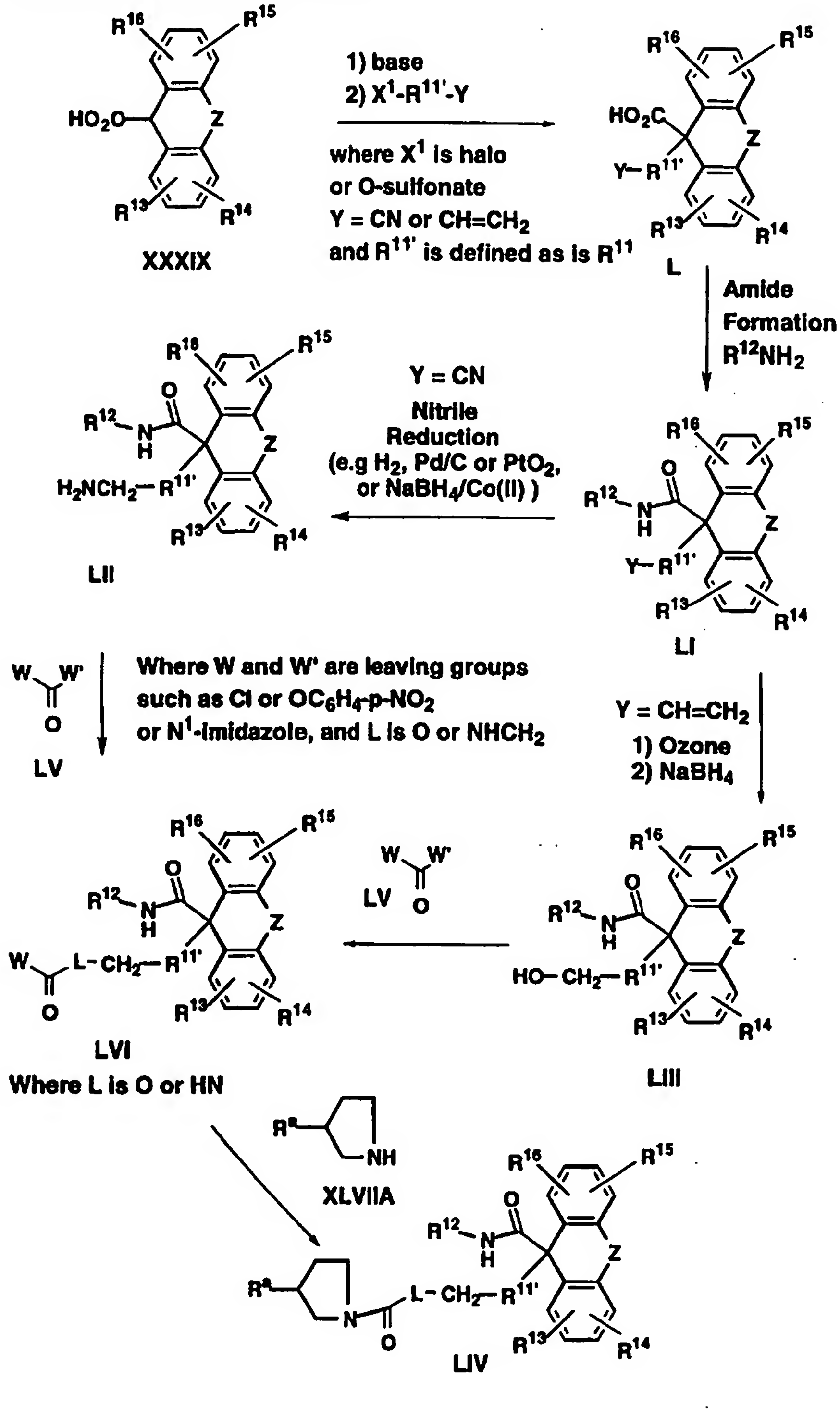



PG is an appropiate protecting group: such as t-butyl(dimethyl)silyl or t-butyl(diphenyl)silyl, which can be deprotected with aqueous acid or n-$Bu_4NF$.

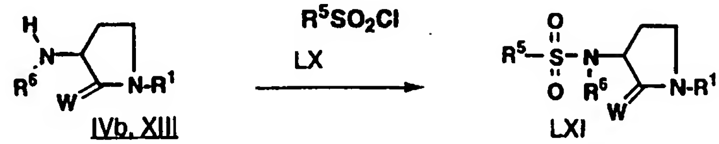
Scheme XVIIA - Preparation of Amide Linked Compounds



Scheme XVIIB - Preparation of Carbamate and Urea Linked Compounds (where W is H,H)

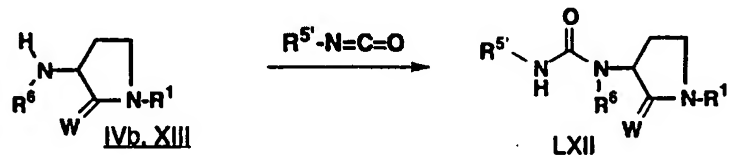


Scheme XVIIIA - Formation of Sulfonamides




(Reaction in a variety of solvents ($CH_2Cl_2$, THF, pyridine) optionally in the presence of a tertiary amine base, such as pyridine or triethyl amine).

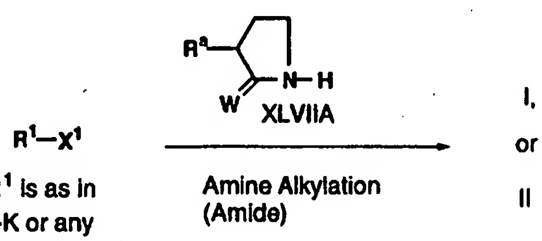
Scheme XVIIIB - Formation of Ureas ($R^5$ is Amino)




(1 to 10 equiv of R-C=N=O, in aprotic solvent such as toluene, from 0°C to 150°C).

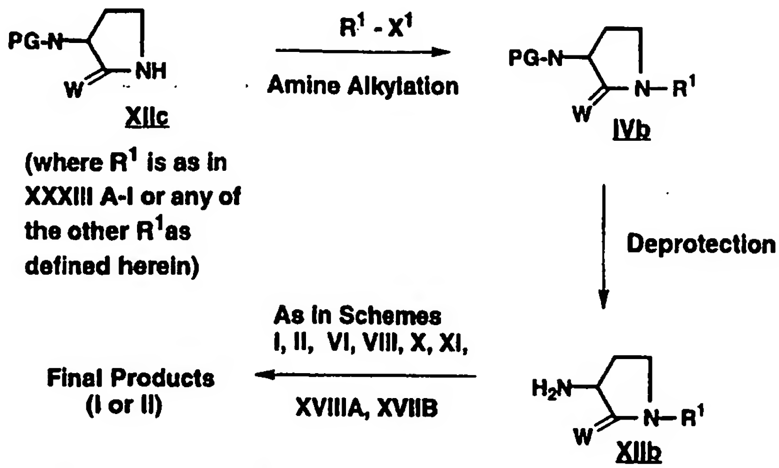
($R^{5'}$ is alkyl, aryl, heteroaryl or arylalkyl).

Scheme XIXA - General Route to Final Product



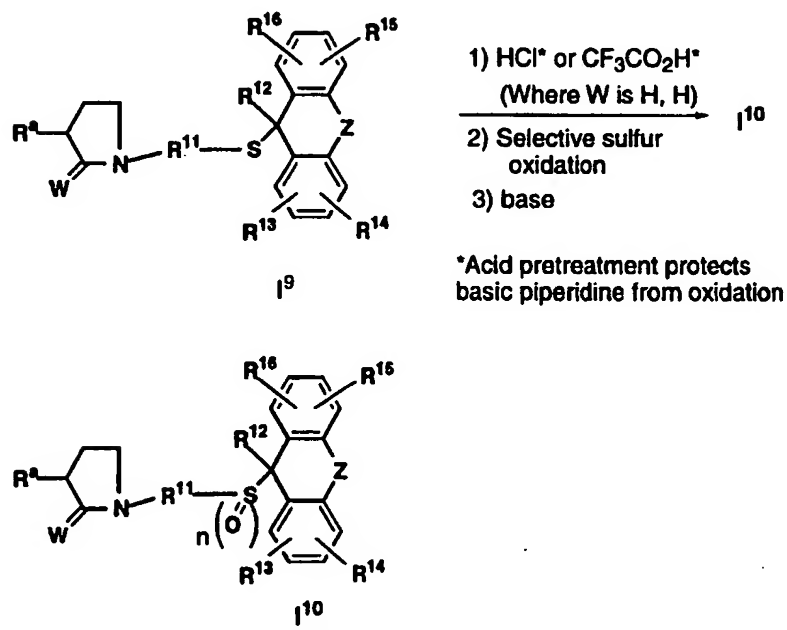

(where $R^1$ is as in XXXIII A-K or any other $R^1$ as defined herein)

Scheme XIXB General Route to Final Products (I or II)




(Example of a protected nitrogen (PG-N) is the t-BuOC=ONH (BOC amino) group, which can be deprotected under mild conditions, such as anhydrous HCl in dioxane or neat trifluoroacetic acid).

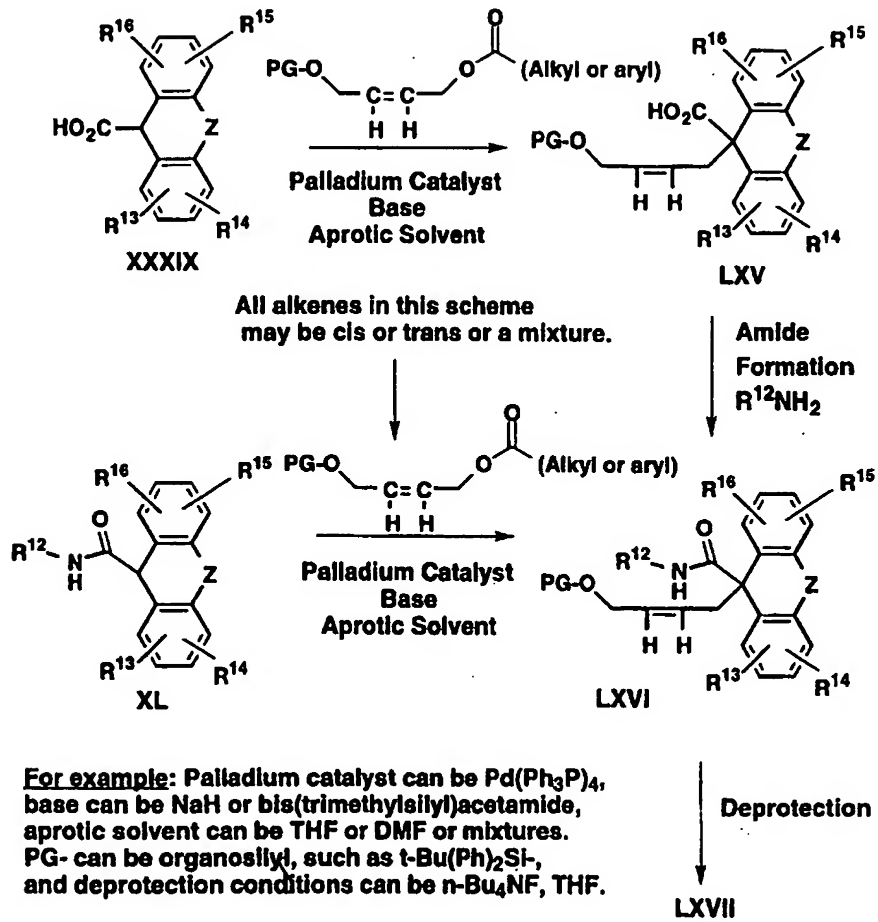
Scheme XX - Oxidation of sulfur at the end of the reaction sequence

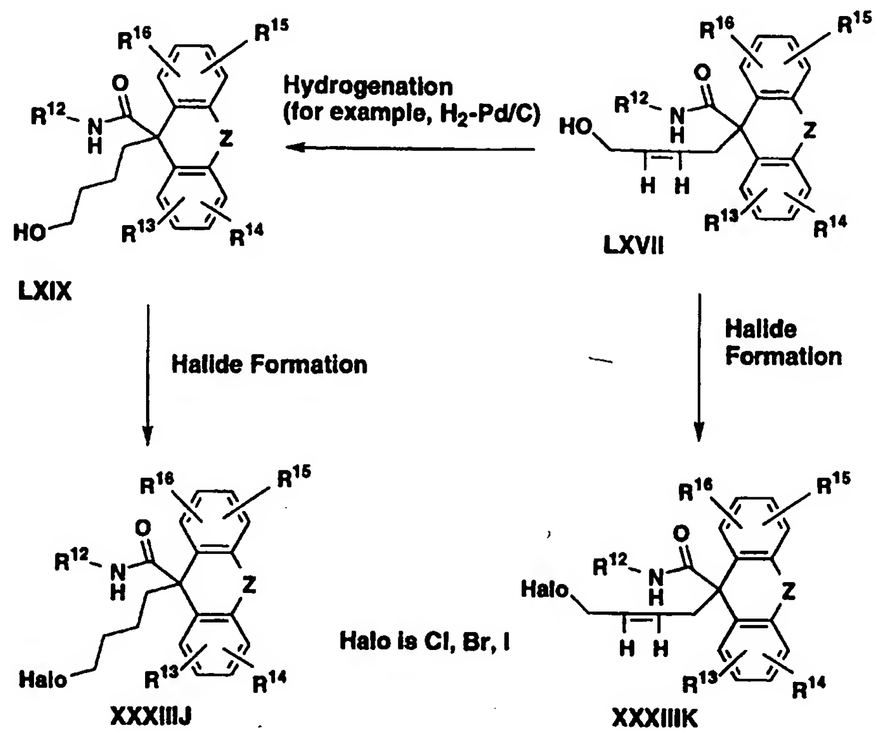



n = 1 or 2

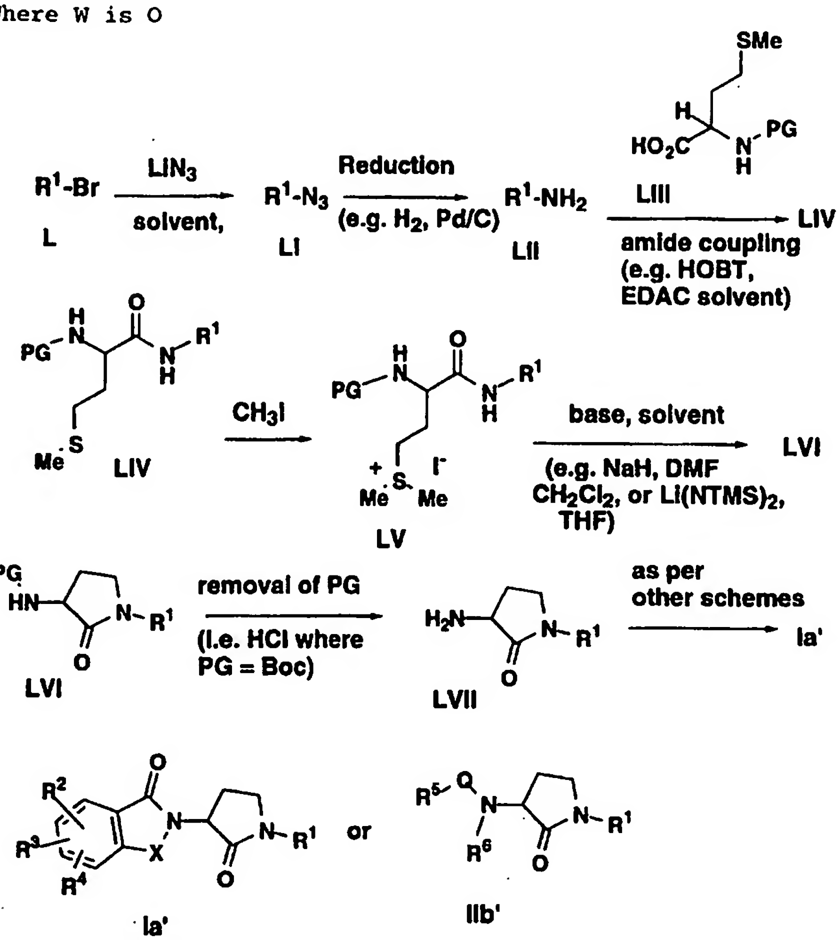
($R^8$ is defined as in Scheme XVIIA)

Scheme XXI - Preparation of Halide Intermediates

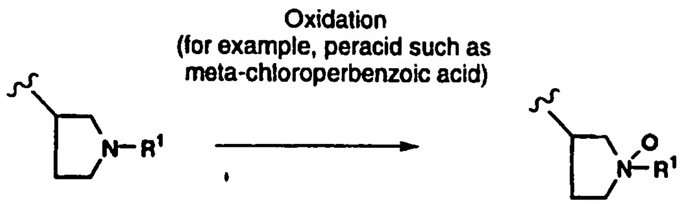



R16
R15
O
R12
N
H
Z
HO
R13
R14
LXIX
Hydrogenation
(for example, H2-Pd/C)
HO
H H
LXVII
Halide Formation
Halide
Formation
Halo
XXXIIIJ
Halo is Cl, Br, I
XXXIIIK

Scheme XXII - Preparation of Formulae I and II Compounds Where W is O



Scheme XXIII - Preparation of N-Oxides of Formulae I and II Compounds




In the above Reaction Schemes XII through XXI, the starting fluorenyl-type acid XXVIII, alcohol XXXV, acids XXXIX and XLII, ketone XLIV, hydride XXXIXA, and amide XL groups may be substituted with corresponding acid, alcohol, ketone, hydride and amide containing fluorenyl type groups as set out in A, B, C and D or indenyl-type groups as set out in E, F, G and/or H to provide an intermediate compound for use in preparing a compound of formula I or II of the invention as per Reaction Schemes I to XXII.

Phthalimide formation (Reaction Schemes I, IV and XXII) may be carried out by heating to about 80 to 150°C in an oil bath optionally in an inert solvent or by various other procedures known in the art.

Reduction (Reaction Schemes I, XXII) may be carried out by treatment with such reducing agents as zinc in the presence of acetic acid or tin in the presence of hydrochloric acid under an inert atmoshphere (e.g., argon).

Isoindolone formation (Reaction Schemes I, XXII) may be carried out by heating in the range of about 50 to 150°C in an organic solvent (e.g., toluene, ethanol, dimethylformamide) optionally in the presence of a salt (e.g., potassium carbonate) or a tertiary amine base (e.g., 2,6-di-t-butyl-pyridine or triethylamine).

Amide formation (Reaction Schemes II, VI, VII, VIII, X, XI, XIVA, XV, XVI, XVIA, XVIB, XVIIA, XVIIB, XXI, XXII), may be carried out by a number of methods known in the art. For example, an amine substrate may be treated with (1) an acid halide $R^5C(O)$halo or compound X or XA in an aprotic solvent, optionally in the presence of a tertiary amine base (e.g., triethylamine); (2) the acid halide in the presence of an aqueous base under Schotten-Baumann conditions; (3) a free carboxylic acid ($R^5CO_2H$) in the presence of a coupling agent such as dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC), optionally in the presence of 1-hydroxybenzotriazole (HOBT); (4) the free acid in the presence of N, N-carbonyldiimidazole in an aprotic organic solvent followed by the amine substrate; (5) trialkylaluminum (e.g., $Al(CH_3)_3$) in an aprotic solvent, followed by an ester (e.g., $R^5CO_2$alkyl or compound VIII) or (6) mixed anhydride formation, by reacting the acid with an acid chloride (e.g., isobutyl chloroformate or bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (Bop-Cl)) in the presence of a tertiary amine base (e.g., triethylamine) followed by treatment with the amine substrate.

Mesylate formation (Reaction Scheme II) may be carried out by treatment of the amine-alcohol substrate with methanesulfonyl chloride and triethylamine or pyridine or in an aprotic solvent, such as dichloromethane.

Base cyclization (Reaction Schemes II, VIII, XXII) may be carried out by treatment with a base (e.g., potassium t-butoxide, lithium hexamethyldisilazide ($LiN(TMS)_2$) or sodium hydride) in an inert solvent (e.g., dimethylformamide,

tetrahydrofuran, dimethoxymethane, or toluene). Mitsunobu cyclization (Reaction Scheme II) may be carried out by procedures generally known in the art. See, e.g., R. K. Olsen, J. Org. Chem., 49, 3527 (1984); Genin, M. J., et al., J. Org. Chem., 58, 2334-7 (1993).

Alternatively, a mixture of compounds IV and VIII can be converted to compound Ia in a single pot by heating the mixture in a protic solvent (e.g., water, methanol, ethenyl or isopropanol or mixtures thereof) at 100 to 200°C. See, e.g., European patent application 81/26,749, FR 2,548,666 (1983).

Protection and deprotection (Reaction Schemes III, IV, V, XVI, XVIB, XIXB, XXI, XXII) may be carried out by procedures generally known in the art. See, for example, T. W. Greene, Protecting Groups in Organic Synthesis, Second edition, 1991. PG in Scheme V denotes a nitrogen-protecting group. One particularly useful group is tert-butoxycarbonyl (BOC) which can be derived from the associated anhydride as shown in Scheme IV. BOC-protected amines may typically be deprotected by treatment with acid (e.g., trifluoroacetic acid or hydrochloric acid) in procedures well understood by those having ordinary skill in the art.

Hydrogenolysis (Reaction Schemes III, IV, V) may be carried out with $H_2$ using a balloon apparatus or a Parr Shaker in the presence of a catalyst (e.g., palladium on activated carbon).

Amine/Amide alkylation and arylation (Reaction Schemes III, IV, V, IX, XII, XIXA, XIXB) may be carried out by methods known in the art. Suitable procedures are described in Cortizo, L., J. Med. Chem. 34, 2242-2247 (1991). For example, the alkylation or arylation may be carried out by

treating the amine substrate with a halide (e.g., $R^1$-halo) or an oxytosylate (e.g., $R^1$-O-tosylate) in an aprotic solvent (e.g., dimethylformamide), optionally in the presence of a tertiary amine (e.g., triethylamine), an inorganic base (e.g., potassium carbonate, NaH), or lithium hexamethyldisilazide).

Reductive amination may be employed as an alternative to the foregoing amine alkylation and arylation procedures where W is H,H when $R^1$, $R^6$ or $R^7$ is $R^9R^{10}CH$- and $R^9$ and $R^{10}$ are each independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl, or $R^9$ and $R^{10}$ together are alkylene (i.e., $R^9R^{10}CH$- forms a cycloalkyl group). Such reductive amination may be carried out by treating the amine with (a) a ketone or aldehyde ($R^9$-C(O)-$R^{10}$), (b) $NaBH_4$, $NaBH_3CN$ or NaB(acetoxy)$_3$H, (c) a protic solvent (e.g., methanol) or a dipolar aprotic solvent (e.g., acetonitrile), and, optionally, (d) an acid (e.g., acetic acid, trifluoroacetic acid, hydrochloric acid, or titanium isopropoxide). When $R^1$ is aryl or heteroaryl, transition metals (e. g., palladium or copper salts or complexes) may be used to promote the arylation reaction.

Alkylation of the isoindolone (Reaction Scheme X, XXII) may be carried out by treatment of the isoindolone with a strong base (i.e. sodium bis(trimethylsilyl)amide or lithium diisopropylamide) followed by an alkyl halide (e.g. $R^8$-halo) or alkyl sulfonate (e.g. $R^8$-tosylate) in an inert solvent (e.g. tetrahydrofuran or dimethoxyethane). Alternatively, as seen in Scheme X, amine IVb can be treated under amide formation conditions with a ketone with the structure XB to provide a hydroxylactam XXV, which could be

subjected to reduction conditions with such reducing agents as zinc in acetic acid or triethylsilane in trifluoroacetic acid to give $I^a$.

Hydrazinolysis of phthalimides may be carried out by standard means known in the art. See, e.g., T. W. Greene, Protecting Groups in Organic Synthesis, Second edition, 1991.

Amide N-alkylation (Reaction Scheme VI, XXII) may be carried out by base treatment (e.g., NaH, KH, $KN[Si(CH_3)_3]_2$, $K_2CO_3$, P4-phosphazene base, or butyl lithium) in an aprotic organic solvent, followed by treatment with $R^6$-halo or $R^6$-O-tosylate. Use of P-phosphazene base is described in T. Pietzonka, D. Seebach, Angew. Chem. Int. Ed. Engl. 31, 1481, 1992.

Compound III can also be prepared from compound XX as described by Cortizo, L., J. Med. Chem. 34, 2242-2247 (1991).

Dehydration (Scheme VIII) may be carried out employing a strong acid such as hydrochloric acid, sulfuric acid or trifluoroacetic acid.

Hydrogenation (Scheme VIII) may be carried out in the presence of a conventional catalyst such as Pd/C or Pt or Rh under a $H_2$ atmosphere.

The addition reaction shown in Scheme IX may be carried out by treating $IA^1$ with an organometallic reagent XXIV, such as an organolithium or organic magnesium compound where organo is alkyl or aryl.

The deoxygenation or hydrogenation reaction (Scheme IX) is carried out in the presence of a strong acid such as trifluoroacetic acid or boron trifluoride etherate, in the presence of a hydride source such as triethyl silane or tris(trimethylsilyl)silane.

The alkylation in Schemes XII, XIII, XIV, XVI, XVIA, XVIB is carried out in the presence of

base such as butyllithium or sodium bis(trimethylsilyl)amide. It will be appreciated that $R^{12}$ in $R^{12}Q$ may be any of the $R^{12}$ groups as defined hereinbefore.

Alternatively, the alkylation in the above Schemes can be performed where either or both $Z^1$ or $Z^2$ is a bond, using a palladium catalyzed allylic alkylation procedure. In this reaction, the fluorenyl-type or indenyl-type precursors (compounds XXVIII, XXXVI, XXXVII, XXXIX, XL, XLVII) are reacted with a base (sodium hydride, sodium bis(trimethylsilyl)amide or bis(trimethylsilyl)acetamide), a palladium catalyst (for example $Pd(Ph_3)_4$) and an allylic acetate ($CH_3CO_2CH_2\text{-}CH{=}CH\text{-}$ or $CH_3CO_2CH(\text{-})\text{-}CH{=}CH_2$) in an inert solvent (for example THF). This reaction is to introduce either $-R^{12}$ (Scheme XII) or $-R^{11}-X^1$ (Schemes XIII, XIV, XVI, XVIA) or $-R^{11}$-OPG (Scheme XVIB, Scheme XXI). The product of this reaction contains either an $-R^{12}$ group or an $-R^{11}-X^1$ group (or an $-R^{11}$-OPG group) which begins with $-CH_2\text{-}CH{=}CH\text{-}$. Saturation of the alkene in $R^{11}$ or $R^{12}$ can be accomplished by standard catalytic hydrogenation conditions.

With respect to Scheme XII, the $LiAlH_4$ reduction, Swern oxidation, Wittig olefination and halogenation/sulfonation reactions are conventional reactions well known to those skilled in the art.

The sulfur oxidation in Schemes XIII, XVI and XVIII is carried out as follows.

Sulfides of structures XXXVI, XXXVIII, XXXIIIE and $I^9$ can be selectively oxidized to sulfoxides by 1 molar equivalent of reagents known in the art, such as 30% $H_2O_2$, $NaIO_4$, and peracids (e.g., meta-chloroperbenzoic acid). The resulting sulfoxides can be further transformed to

corresponding sulfones by another molar equivalent or excess of 30% $H_2O_2$, $KMnO_4$, $KHSO_5$, or peracids (e.g., meta-chloroperbenzoic acid). Alternatively, the sulfones can be directly prepared from sulfides with 2 molar equivalents or more of oxidizing agents, such as 30% $H_2O_2$ and peracids (e.g., meta-chloroperbenzoic acid). In cases where an amine (such as a pyrrolidine in $I^9$) is present during the oxidation, the basic nitrogen may be protected by pretreatment with an acid such as HCl or $CF_3CO_2H$ (see Scheme XIX).

To prepare examples where $Z^1$ or $Z^2$ is -CHOH, the compounds I and II where $Z^1$ or $Z^2$ is C=O can be reduced with a hydride reagent, for example $NaBH_4$.

The compounds of the invention may be employed in preventing, stabilizing or causing regression of atherosclerosis in a mammalian species by administering a therapeutically effective amount of a compound to decrease the activity of MTP.

The compounds of the invention can be tested for MTP inhibitory activity employing the procedures set out in U.S. application Serial No. 117,362 filed September 3, 1993, employing MTP isolated from one of the following sources:

(1) bovine liver microsomes,

(2) $HepG_2$ cells (human hepatoma cells) or

(3) recombinant human MTP expressed in baculovirus.

The compounds of the invention may also be employed in lowering serum lipid levels, such as cholesterol or triglyceride (TG) levels, in a mammalian species, by administering a therapeutically effective amount of a compound to decrease the activity of MTP.

The compounds of the invention may be employed in the treatment of various other

conditions or diseases using agents which decrease activity of MTP. For example, compounds of the invention decrease the amount or activity of MTP and therefore decrease serum cholesterol and TG levels, and TG, fatty acid and cholesterol absorption and thus are useful in treating hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, pancreatitis, hyperglycemia and obesity.

The compounds of the present invention are agents that decrease the activity of MTP and can be administered to various mammalian species, such as monkeys, dogs, cats, rats, humans, etc., in need of such treatment. These agents can be administered systemically, such as orally or parenterally.

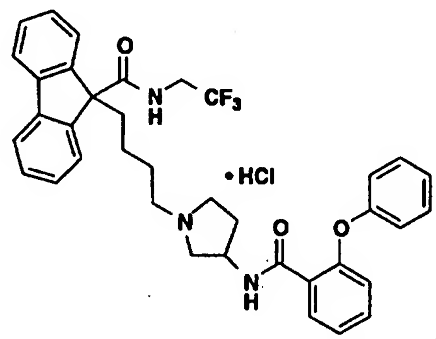
The agents that decrease the activity or amount of MTP can be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physiologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms described above may be administered in amounts of from about 5 to about 500 mg per day in single or divided doses of one to four times daily.

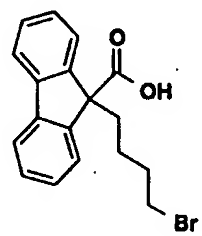
The following Examples represent preferred embodiments of the invention. All temperatures are in °C unless indicated otherwise.

## Example 1

9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride



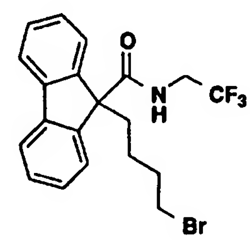

A.




To a solution of 9-fluorenecarboxylic acid (50 g, 240 mmol) in THF (1200 mL) at 0°C was added dropwise a solution of n-butyllithium (2.5M, 211 mL, 530 mmol) in THF. The yellow reaction was stirred at 0°C for 1 h, then 1,4-dibromobutane (31.3 mL, 260 mmol) was added dropwise over 30 min. The reaction was stirred at 0°C for 30 min, then the reaction was warmed to RT for 30 h. The reaction was extracted with water (3 x 750 mL). The combined aqueous layers were extracted with ethyl ether (800 mL). The aqueous layer was made acidic with HCl solution (1N, 500 mL), then

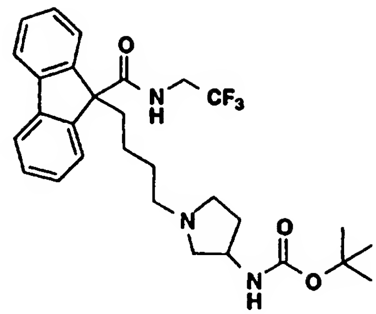
extracted with dichloromethane (3 x 750 mL). The combined organic layers were dried over $MgSO_4$. Evaporation gave title compound (71 g, 85%) as a white solid.

B.



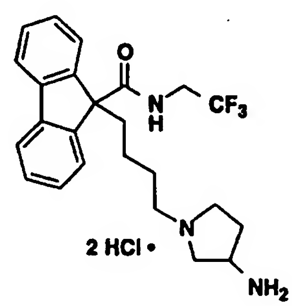
To a solution of Part A acid (60 g, 173 mmol) and DMF (100 µL) in $CH_2Cl_2$ (600 mL) under argon at 0°C was added oxalyl chloride (104 mL, 2.0M in $CH_2Cl_2$, 208 mmol) dropwise. The reaction was stirred at 0°C for 10 min, then warmed to RT and stirred for 1.5 h. The reaction was concentrated in vacuo to give the crude acid chloride as a yellow oil. To a suspension of 2,2,2-trifluoroethylamine hydrochloride (25.9 g, 191 mmol) in $CH_2Cl_2$ (500 mL) at 0°C under argon was added triethylamine (73 mL, 521 mmol) followed by dropwise addition of a solution of the crude acid chloride in $CH_2Cl_2$ (15 mL). The reaction was stirred at 0°C for 1 h, diluted with $CH_2Cl_2$ (500 mL), and washed with water (2 x 300 mL), 1N HCl (2 x 300 mL), saturated $NaHCO_3$ (2 x 300 mL), and brine (2 x 300 mL), then dried over $MgSO_4$. Evaporation gave 80 g of a oil which was purified by flash chromatography on silica gel (2.5 kg). The crude product was loaded in a mixture of $CH_2Cl_2$ and hexane, and eluted with a step gradient of 10% EtOAc/hexane (4L) to 15% EtOAc/hexane (2L) to 20% EtOAc/hexane (4L). Pure fractions were combined and evaporated to give title compound (52.5 g, 71%) as a white solid (mp 88-92°C).

C.



A mixture of Part B compound (732 mg, 1.72 mmol), 3-(tert-butoxycarbonylamino)-pyrrolidine (383 mg, 2.06 mmol), and anhydrous potassium carbonate (356 mg, 2.58 mmol) in DMF (5 mL) was heated at 50°C under argon overnight (18 h), cooled to RT, and the solvent removed under high vacuum. The residue was partitioned between $CH_2Cl_2$ (20 mL) and water (5 mL). The organic layer was washed with water (5 mL), dried over $Na_2SO_4$, and evaporated to give 1.2 g of an orange solid. The crude product was purified by flash chromatography on silica gel (70 g) eluting with 5% MeOH/$CH_2Cl_2$ to provide title compound (673 mg, 74%) as a white foam.

D.



To a solution of Part C compound (625 mg, 1.18 mmol) in dioxane (2 mL) was added 4N HCl in dioxane (2 mL, 8 mmol). The clear solution was stirred at RT for 3 h, concentrated in vacuo, and

pumped under high vacuum overnight to give title compound (646 mg, >100%) as a white foamy solid.

E. 2-Phenoxybenzoic acid chloride

To a solution of 2-phenoxybenzoic acid (Aldrich) (500 mg, 2.33 mmol) and DMF (1 drop) in dichloromethane (10 mL) at RT was added dropwise a solution of oxalyl chloride in dichloromethane (2.0M, 1.28 mL, 2.56 mmol). Bubbling of escaping gasses continued for 10 min after addition. The reaction was stirred at RT for 60 min, then concentrated in vacuo to give title compound as an oil.

F. 9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoro-ethyl)-9H-fluorene-9-carboxamide, monohydrochloride

A solution of Part D compound (350 mg, 0.696 mmol) in $CH_2Cl_2$ (2 mL) was cooled to 0°C under argon. Triethylamine (385 µL, 2.78 mmol) was added, which gave a cloudy mixture. A solution of Part E acid chloride in $CH_2Cl_2$ (1.5 mL) was added and the reaction mixture was stirred at 0°C for 10 min, diluted with $CH_2Cl_2$ (2 mL), washed with water (2 mL) and saturated $NaHCO_3$ (2 mL), dried over $Na_2SO_4$, and then evaporated to give 450 mg of a gold-colored gum. The crude product was purified by flash chromatography on silica gel (50 g) eluting with 4% $MeOH/CH_2Cl_2$ to provide 360 mg of the free amine as a white foam.

To a solution of the free amine in THF (3 mL) was added 1.1N HCl in $Et_2O$ (1.0 mL, 1.1 mmol). The reaction mixture was concentrated in vacuo, and the residue was triturated with $Et_2O$. The resulting foam was dried in a vacuum oven (50°C,

0.2 torr) overnight to provide title compound (380 mg, 82%) as a foamy tan solid.

MS (ES, + ions) m/z 628 (M+H)
Anal. Calc'd for $C_{37}H_{37}F_3N_3O_3$ + $0.6H_2O$:
C, 65.84; H, 5.70; N, 6.23; F, 8.44
Found: C, 66.20; H, 5.60; N, 6.13; F, 8.04.

**Example 2**

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

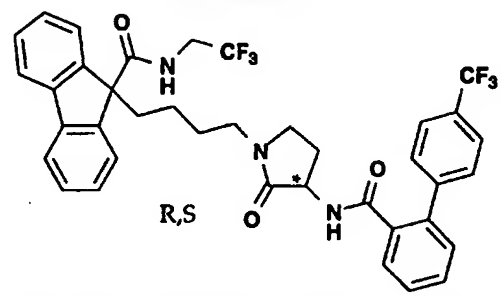
To a mixture of Example 1 compound (273 mg, 0.543 mmol) and triethylamine (300 µL, 2.17 mmol) in $CH_2Cl_2$ (2 mL) at 0°C under argon was added benzoyl chloride (70 µL, 0.597 mmol). The reaction mixture was stirred at 0°C for 15 min, diluted with $CH_2Cl_2$ (3 mL), washed with water (1 mL) and saturated $NaHCO_3$ (2 mL), and then dried over $Na_2SO_4$. Evaporation of the filtrate gave a brown foam, which was purified by flash chromatography on silica gel (60 g) eluting with 3% MeOH/$CH_2Cl_2$ to provide 196 mg of product as the free amine.

A portion of the desired product (176 mg) was dissolved in MeOH (2 mL) and a solution of 1.1N HCl/$Et_2O$ (0.6 mL, 0.66 mmol) was added. The solution was concentrated in vacuo and the residue was triturated with $Et_2O$ to give a foamy solid, which was pumped under high vacuum overnight to afford title compound (175 mg, 62%) as a foamy white solid.
MS (ES, + ions) m/z 536 (M+H)

Anal. Calc'd for $C_{31}H_{33}Cl_3N_3O_2$ + $0.4H_2O$:
C, 64.28; H, 5.88; N, 7.25; Cl, 6.12; F, 9.84

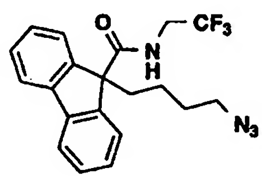
Found: C, 64.27; H, 5.93; N, 7.29; Cl, 5.71; F, 9.73.

## Example 3



9-[4-[2-Oxo-3-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

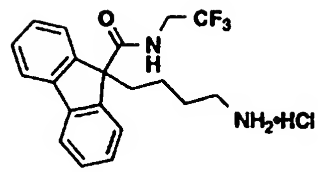
A.



A slurry of Example 1 Part B bromide (3.037 g, 7.12 mmol) and $NaN_3$ (2.26 g, 34.7 mmol) in DMF (15 mL) was heated at 50°C for 3 hours and then at 95°C for 2 hours. The mixture was cooled to room temperature and partitioned between EtOAc and $H_2O$. The organic layer was washed successively with $H_2O$, 1 N HCl, $H_2O$, and brine, then dried ($Na_2SO_4$), filtered and stripped to give a yellow oil which slowly solidified. Recrystallization from hexane afforded title azide compound (2.198 g) as a white solid. An additional 212 mg of material was obtained from the mother liquor to give a total of 2.41 g (87%) of title azide.

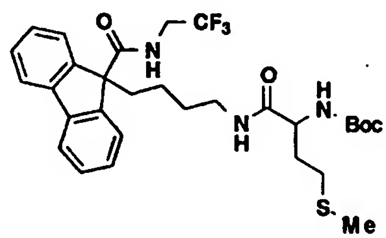
mp: 84-86°C.

B.



A solution of Part A azide (2.253 g, 5.8 mmol) in MeOH (40 mL) was hydrogenated (balloon) over palladium (10% Pd on carbon, 250 mg) at room temperature for 1 hour. The mixture was filtered through Celite and the filtrate was stripped, re-dissolved in MeOH, and treated with 4 N HCl in dioxane. Trituration with $Et_2O$ followed by collection of the precipitate and drying in vacuo afforded title compound (2.090 g, 90%) as a grayish white solid.
mp: 200-202°C.

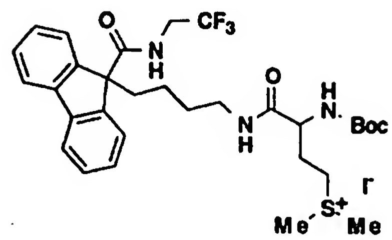
C.



A solid mixture of Part B compound (2.048 g, 5.1 mmol), N-Boc-D,L-methionine (1.280 g, 5.1 mmol), and HOBT•$xH_2O$ (693 mg) was slurried in $CH_2Cl_2$ and subsequently treated with N-methyl-morpholine (0.9 mL, 828 mg, 8.2 mmol) followed by ethyl-3-(3-dimethylamino)propyl carbodiimide •HCl salt (EDAC) (1.083 g, 5.6 mmol). After stirring at room temperature for 18 hours, the homogeneous mixture was partitioned between EtOAc/$Et_2O$ and 1 N HCl. The organic layer was washed with $H_2O$, 50% saturated $NaHCO_3$, and brine, then dried ($Na_2SO_4$), filtered and stripped to give racemic title compound (2.972 g, 98%) as a foam.

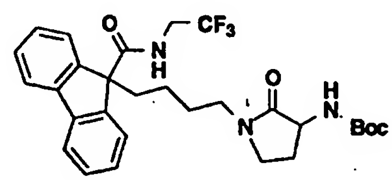
TLC: $R_f$ 0.44 (6/4-EtOAc/hexanes).

D.



Part C compound (2.902 g, 4.88 mmol) was dissolved in $CH_3I$ (35 mL) and stirred at room temperature for 2 days. The solvent was stripped, then triturated and stripped from hexane twice to give crude title compound (3.74 g, 104% of theory) as a pale yellow solid which was used directly in the next reaction without further purification.

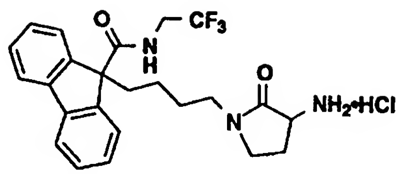
E.



A solution of Part D sulfonium salt (3.069 g, 4.17 mmol) in DMF (20 mL) and $CH_2Cl_2$ (22 mL) at 0°C was treated all at once with solid NaH (60% in mineral oil, 400 mg, 240 mg pure, 10.0 mmol). After stirring at 0°C for 1.5 hours and at room temperature for 1.5 hours, the mixture was quenched with 0.5 N HCl and extracted with EtOAc. The EtOAc extract was washed twice with $H_2O$, once with saturated $NaHCO_3$, and once with brine, then dried ($Na_2SO_4$), filtered and stripped. Flash chromatography (Merck $SiO_2$, 7/3-EtOAc/hexanes) afforded title compound (1.774 g, 78%) as a white foam.

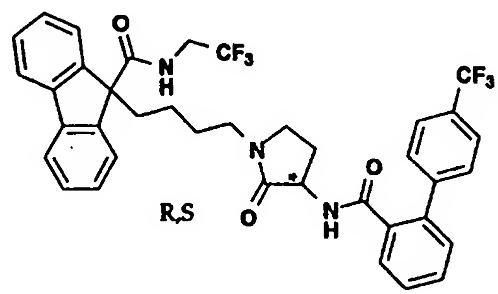
TLC: $R_f$ 0.21 (6/4-EtOAc/hexane).

F.



A solution of Part E compound (1.752 g, 3.2 mmol) in 1,4-dioxane (8 mL) was treated with 4 N HCl in 1,4-dioxane (5 mL). After 5 hours, the solvent was stripped and the residue was azeotroped twice from $CH_2Cl_2/Et_2O$ and triturated from $Et_2O$/hexane. The solid was collected by filtration and dried in vacuo to give title compound (1.576 g, 102% of theory) as a white solid.

G.



A solid mixture of Part F compound (250 mg, 0.52 mmol), 4'-(trifluoromethyl)-2-biphenylcarboxylic acid (145 mg, 0.54 mmol), and HOBT•$xH_2O$ (70 mg) was slurried in $CH_2Cl_2$ (5 mL) and subsequently treated with N-methyl morpholine (86 uL, 79 mg, 0.78 mmol) followed by EDAC (111 mg, 0.58 mmol). After stirring at room temperature for 18 hours, the mixture was partitioned between EtOAc and 1 N HCl. The EtOAc extract was washed successively with $H_2O$, saturated $NaHCO_3$ and brine, then dried ($Na_2SO_4$), filtered and stripped. Flash chromatography (Merck $SiO_2$, 8/2-EtOAc/hexanes) afforded title compound (310 mg, 86%) as a white foam.

TLC: $R_f$ 0.21 (8/2-EtOAc/hexanes)

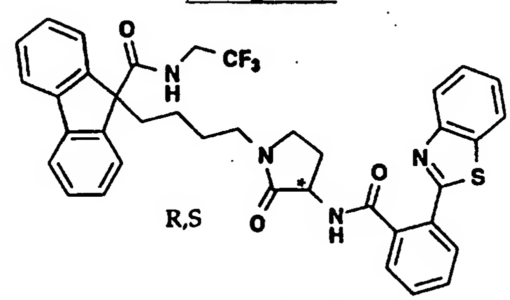
MS: $(M+H)^+$ @ 694; $(M-H)^-$ 692; $(M+NH_4)^+$ 711

HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 0% to 100% B, 30 minute gradient, (A = 90% $H_2O$-10% MeOH-0.2% $H_3PO_4$ and B = 10% $H_2O$-90% MeOH-0.2% $H_3PO_4$) flow rate at 1.5 ml/min detecting at 220 nm; $t_R$ = 30.98 min (98.1%).

Microanalysis Calc'd for $C_{38}H_{33}F_6N_3O_3$ + $0.13CH_2Cl_2$:
C, 64.96; H, 4.76; N, 5.96; F, 16.17; Cl, 1.35

Found: C, 64.86; H, 4.80; N, 5.89; F, 16.22; Cl 1.34.

**Example 4**



9-[4-[3-[[2-(2-Benzothiazolyl)benzoyl]amino]-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

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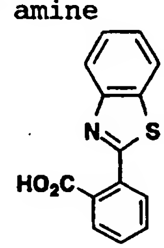
A slurry of Example 3 Part F amine hydrochloride (200 mg, 0.415 mmol),  (98 mg, 0.38 mmol), and HOBT•$xH_2O$ (56 mg) in $CH_2Cl_2$ (5 mL) was treated successively with N-methyl morpholine (70 µL, 65 mg, 0.65 mmol) and EDAC (89 mg, 0.46 mmol) at room temperature. After 18 hours, the mixture was partitioned between EtOAc and saturated $NaHCO_3$. The EtOAC extract was washed successively with $H_2O$, 1 N HCl, and brine, then

dried ($Na_2SO_4$), filtered, and stripped repeatedly from $CH_2Cl_2$ to give title compound (249 mg, 95%) as a white foam.

TLC: $R_f$ 0.19 (EtOAc)

MS: $(M+H)^+$ @ 683; $(M-H)^-$ 681

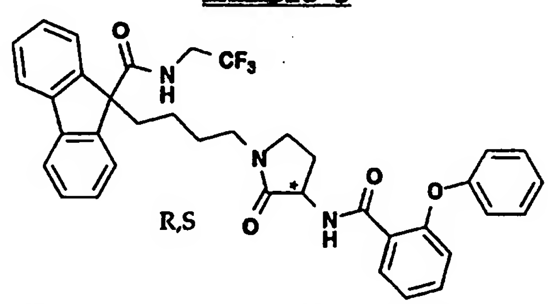
HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% $H_2O$-10% MeOH-0.2% $H_3PO_4$ and B = 10% $H_2O$-90% MeOH-0.2% $H_3PO_4$) flow rate at 1.5 ml/min detecting at 254 nm; $t_R$ = 18.9 min (96.6%).

Microanalysis Calc'd for $C_{38}H_{33}F_3N_4O_3S$+0.09 $CH_2Cl_2$:

C, 66.27; H, 4.84; N, 8.12; F, 8.26;
S, 4.64; Cl, 0.92

Found: C, 65.92; H, 3.92; N, 7.81; F, 7.98;
S, 4.56; Cl, 0.70.

## Example 5




9-[4-[2-Oxo-3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

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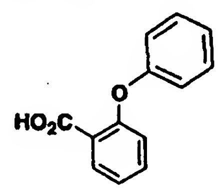
A slurry of Example 3 Part F amine hydrochloride (200 mg, 0.415 mmol),

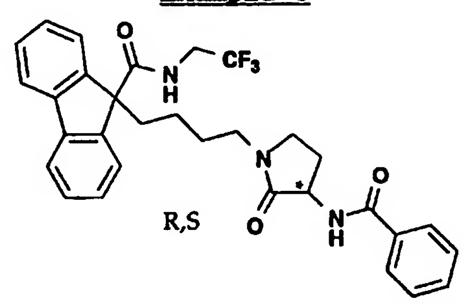


(85 mg, 0.40 mmol), and HOBT•x$H_2O$ (56 mg) in $CH_2Cl_2$ (7 mL) was treated successively with N-methyl morpholine (70 µL, 65 mg, 0.65 mmol) and EDAC (89 mg, 0.46 mmol) at room temperature. After 22 hours, the mixture was partitioned between EtOAc and saturated $NaHCO_3$. The EtOAC extract was washed

successively with $H_2O$, 1 N HCl, and brine, then dried ($Na_2SO_4$), filtered, and stripped repeatedly from $CH_2Cl_2$ to give title compound (224 mg, 87%) as a white foam.

TLC: $R_f$ 0.46 (EtOAc)
MS: $(M+H)^+$ @ 642; $(M-H)^-$ 640
HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% $H_2O$-10% MeOH-0.2% $H_3PO_4$ and B = 10% $H_2O$-90% MeOH-0.2% $H_3PO_4$) flow rate at 1.5 ml/min detecting at 254 nm; $t_R$ = 19.7 min (100%).
Microanalysis Calc'd for $C_{37}H_{34}F_3N_3O_4$:
C, 69.26; H, 5.34; N, 6.55; F, 8.88
Found: C, 68.92; H, 5.25; N, 6.42; F, 8.70.

## Example 6




9-[4-[3-(Benzoylamino)-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

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A solution of Example 3 Part F amine hydrochloride (200 mg, 0.415 mmol) and triethylamine (TEA) (200 µL, 145 mg, 1.43 mmol) in $CH_2Cl_2$ (4 mL) at 0°C was treated with benzoyl chloride (48 µL, 58 mg, 0.41 mmol). After 45 minutes, the mixture was quenced with saturated $NaHCO_3$ and extracted with EtOAc. The EtOAc extract was washed successively with $H_2O$, 1 N HCl, $H_2O$, and brine, then dried ($Na_2SO_4$), filtered and stripped to give title compound (231 mg, 98%) as a white foam.

TLC: $R_f$ 0.35 (EtOAc)

MS: $(M+H)^+$ @ 550; $(M-H)^-$ 548

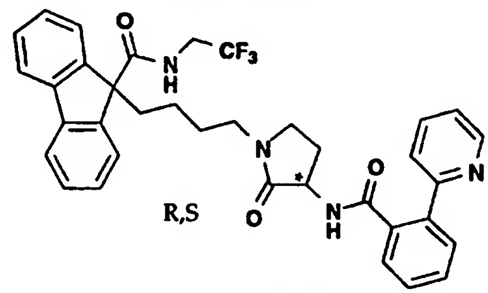
HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% $H_2O$-10% MeOH-0.2% $H_3PO_4$ and B = 10% $H_2O$-90% MeOH-0.2% $H_3PO_4$) flow rate at 1.5 ml/min detecting at 254 nm; $t_R$ = 16.2 min (96.7%).

Microanalysis Calc'd for $C_{31}H_{30}F_3N_3O_3$ + 0.2EtOAc:

C, 67.34; H, 5.62; N, 7.41; F, 9.59

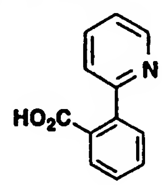
Found: C, 67.15; H, 5.55; N, 7.13; F, 9.73.

## Example 7




9-[4-[2-Oxo-3-[[2-(2-pyridinyl)benzoyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

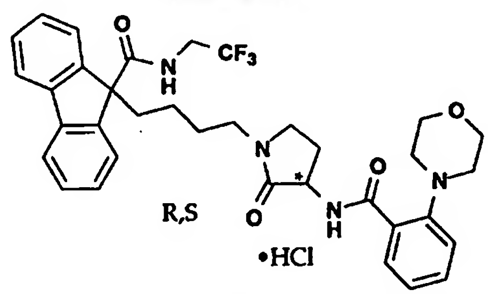
A slurry of Example 3 Part F amine hydrochloride (202 mg, 0.419 mmol),



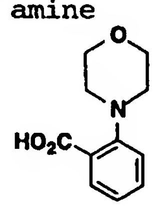

(88 mg, 0.44 mmol), and 1-hydroxy-7-azabenzotriazole (HOAT) (55 mg) in $CH_2Cl_2$ (3 mL) was treated successively with N-methyl morpholine (56 µL, 52 mg, 0.51 mmol) and EDAC (87.5 mg, 0.46 mmol) at room temperature. After 18 hours, the mixture was partitioned between EtOAc and saturated $NaHCO_3$. The EtOAc extract was washed successively with $H_2O$ and brine, then dried ($Na_2SO_4$), filtered, and stripped. The residue was flash chromatographed (Merck $SiO_2$, 5/95-MeOH/$CH_2Cl_2$ as eluant) to give title compound (259 mg, 94%) as a white foam.

TLC: $R_f$ 0.47 (1/9-MeOH/$CH_2Cl_2$)
MS: $(M+H)^+$ @ 627
HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% $H_2O$-10% MeOH-0.2% $H_3PO_4$ and B = 10% $H_2O$-90% MeOH-0.2% $H_3PO_4$) flow rate at 1.5 ml/min detecting at 254 nm; $t_R$ = 11.6 min (98.9%).
Microanalysis Calc'd for $C_{36}H_{33}F_3N_4O_3$+0.35 $CH_2Cl_2$:
C, 66.51; H, 5.18; N, 8.54; F, 8.68
Found: C, 66.88; H, 5.07; N, 8.36; F, 7.91.

## Example 8




9-[4-[3-[[2-(4-Morpholinyl)benzoyl]amino]-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

A slurry of Example 3 Part F amine hydrochloride (200 mg, 0.415 mmol), 

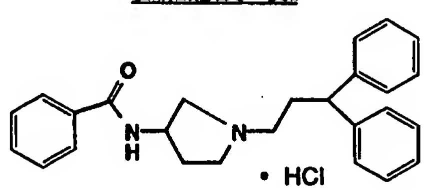
(111 mg, 0.53 mmol), and HOAT (53 mg) in $CH_2Cl_2$ (5 mL) was treated successively with N-methyl morpholine (100 µL, 93 mg, 0.91 mmol) and EDAC (90 mg, 0.47 mmol) at room temperature. After 20 hours, the mixture was partitioned between EtOAc and saturated $NaHCO_3$. The EtOAC extract was washed successively with $H_2O$ and brine, then dried ($Na_2SO_4$), filtered, and stripped to give an oil. The residue was flash chromatographed (Merck $SiO_2$, 5/95-MeOH/$CH_2Cl_2$ as eluant) to give the free base

of title compound (141 mg, 53%) as pale yellow oil. The oil was dissolved in 1,4-dioxane (2 mL), treated with 4 N HCl in 1,4-dioxane (150 µL) and added via cannula to rapidly swirling $Et_2O$ (30 mL). The precipitate was collected by filtration and dried in vacuo to give title compound (101 mg, 35% from Example 3 Part F compound) as a pink solid.

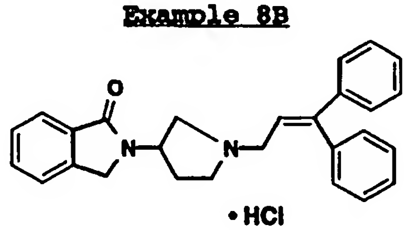
TLC: $R_f$ 0.64 (1/9-MeOH/$CH_2Cl_2$)
MS: $(M+H)^+$ @ 635
HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% $H_2O$-10% MeOH-0.2% $H_3PO_4$ and B = 10% $H_2O$-90% MeOH-0.2% $H_3PO_4$) flow rate at 1.5 ml/min detecting at 254 nm; $t_R$ = 16.9 min (98.7%).

The following Examples represent preferred embodiments of the invention and may be prepared employing procedures described herein.

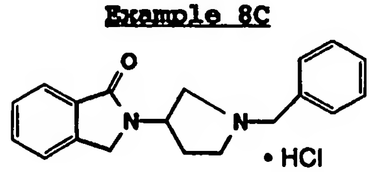
**Example 8A**



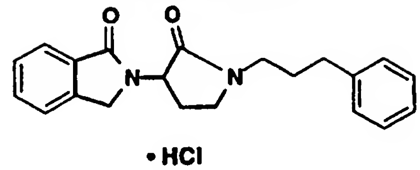

**Example 8B**



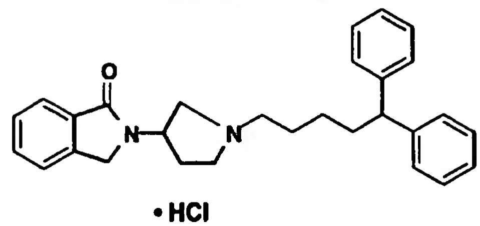

**Example 8C**



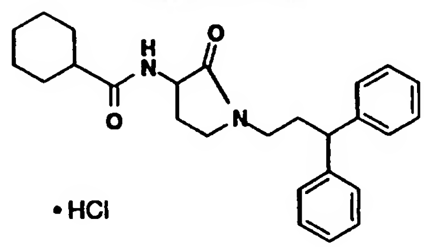
Example 8D



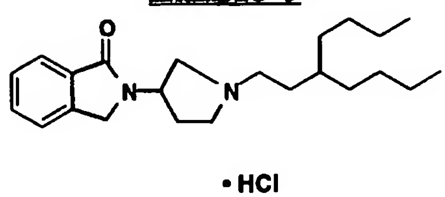

Example 8E



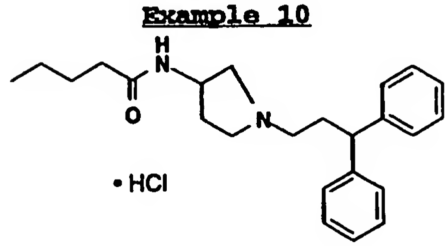

Example 8F



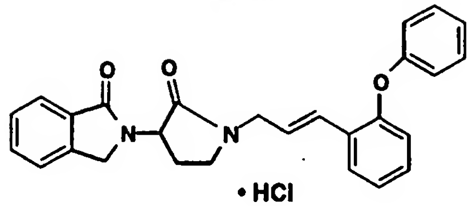

Example 9



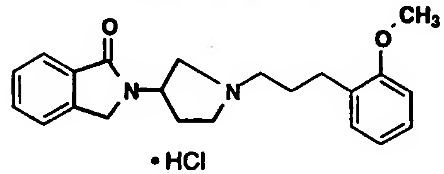

Example 10



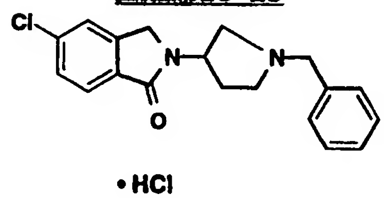
**Example 11**



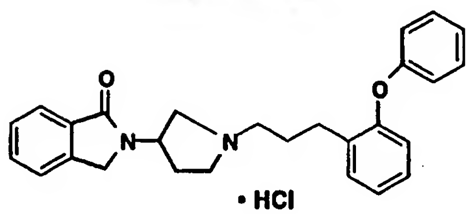
**Example 12**



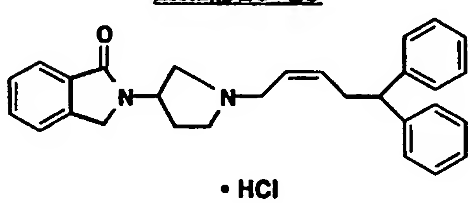
**Example 13**



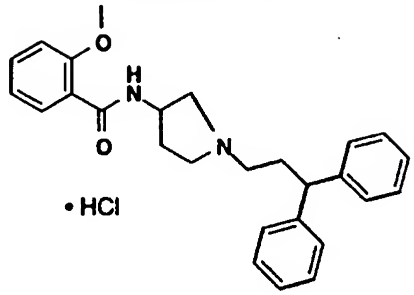
**Example 14**



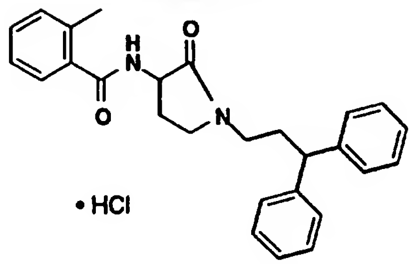
**Example 15**



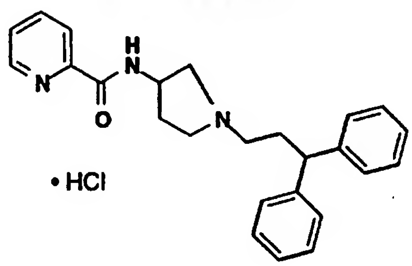
**Example 16**



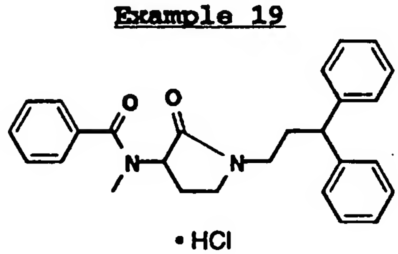

**Example 17**




**Example 18**

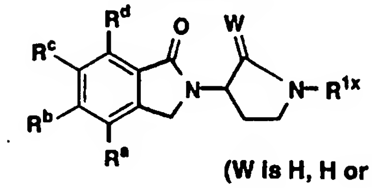



**Example 19**



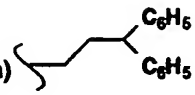
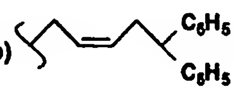
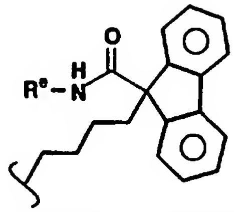
## Examples 20 to 202

### Table A

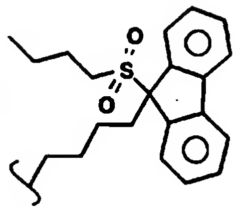
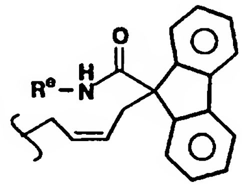


(W is H, H or O)

where $R^{1x}$ is

(a)  , (b)  , (c)  ,

($R^e$=$C_3H_7$ or $CF_3CH_2$)

(d)  or (e) 

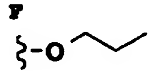
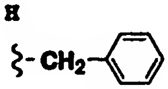
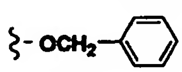
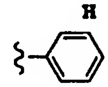
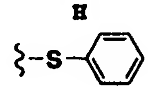
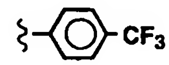
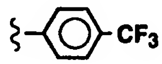
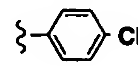
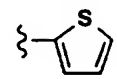
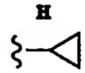
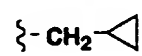
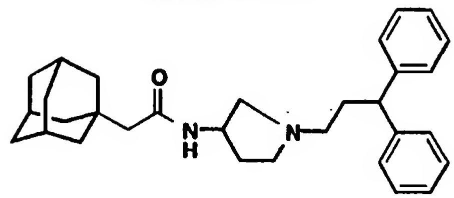
| $R^a$ | $R^b$ | $R^c$ | $R^d$ |
|---|---|---|---|
| H | H | H | F |
| H | H | H |  |
| H | H | F | Cl |
| H | H | $CF_3$ | H |
| H | $OCH_3$ | H | H |
| H | H | H | |
|  | | | |
|  | H | H | H |
| H | H |  | H |
| F | Cl | H | H |
| H | H | H |  |

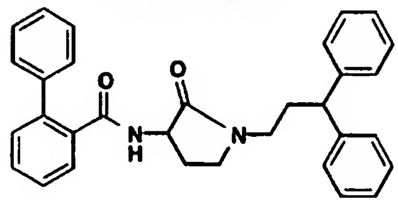
Table A (continued)

| $R^a$ | $R^b$ | $R^c$ | $R^d$ |
|---|---|---|---|
| H | H | H |  |
|  | H | H | H |
| H | H | Cl | H |
| H | H | H |  |
| H | H | H | H |
| H | H | H | Cl |
| H | H | $CH_3$ | H |
| H | CH3 | H |  |
| $SCH_3$ | H | H | H |
| H | H | $OCH_3$ | H |
| H | H | H | $SCH_3$ |
| H | H | H | H |
| H | H | H | $CH_2{-}C\equiv C{-}H$ |
| H |  | H | H |
| H | H | H |  |

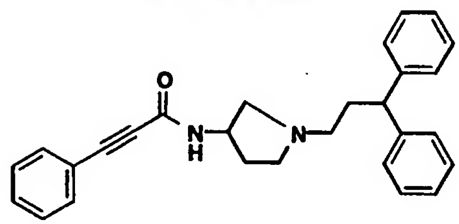
Example 203



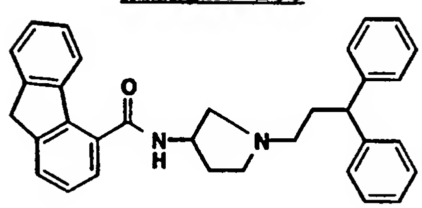
Example 204



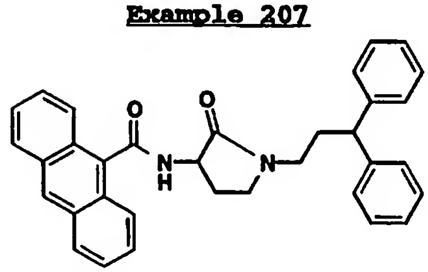
Example 205



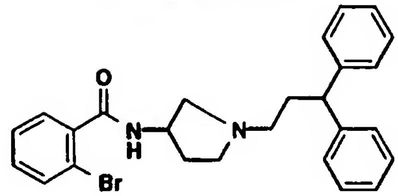
Example 206



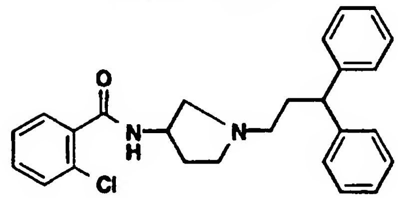
Example 207



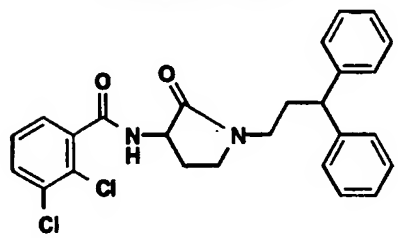
Example 208



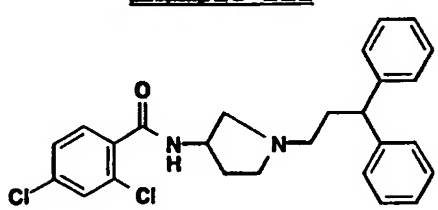
Example 209



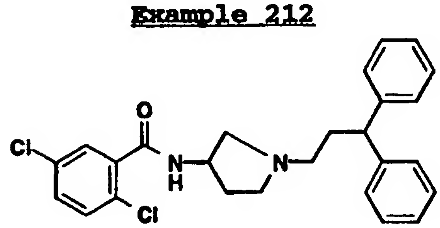
Example 210



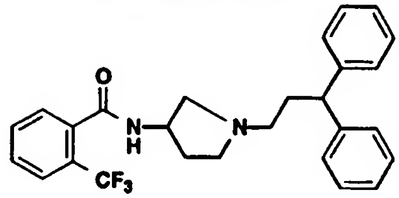
Example 211



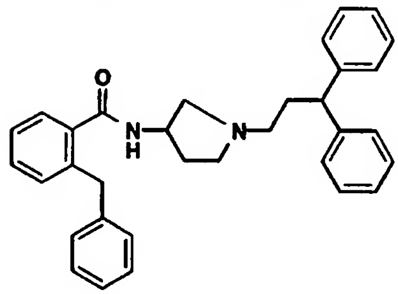
Example 212



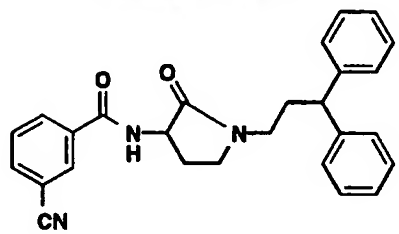
Example 213



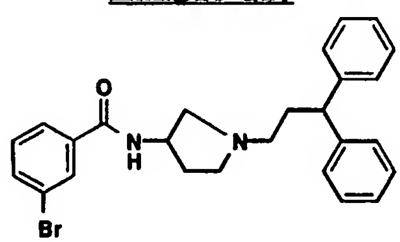
Example 214



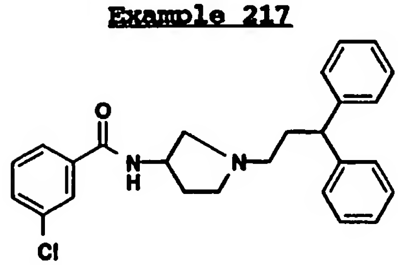
Example 215



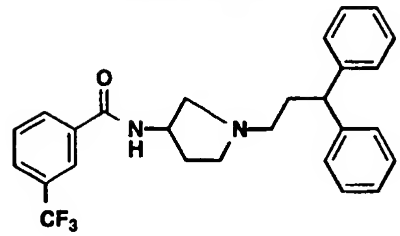
Example 216



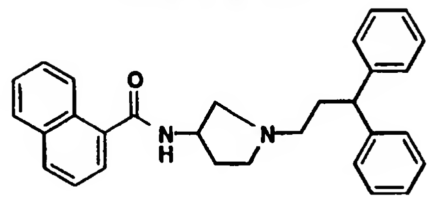
Example 217



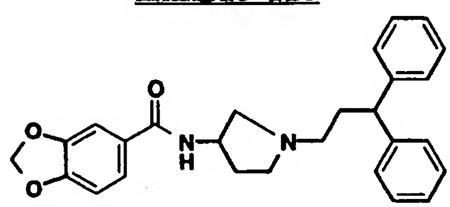
Example 218



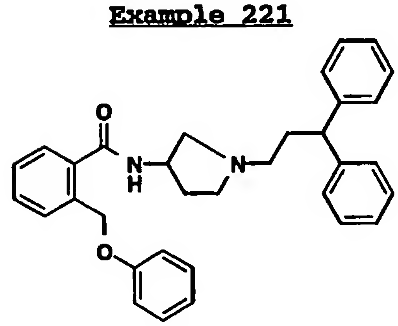
Example 219



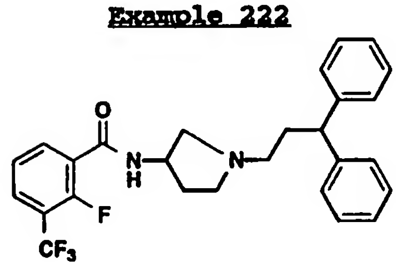
Example 220



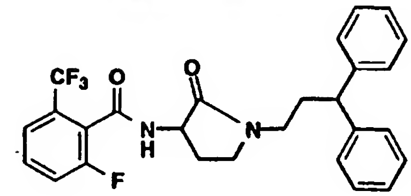
Example 221



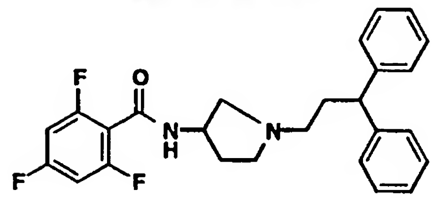
Example 222



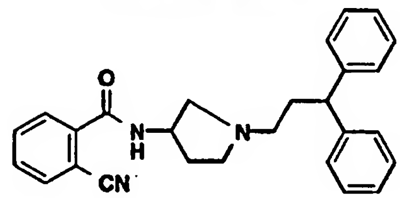
Example 223



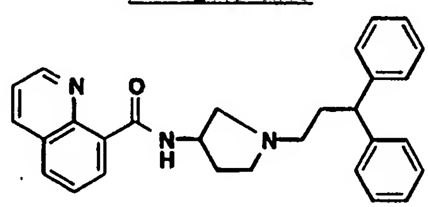
Example 224



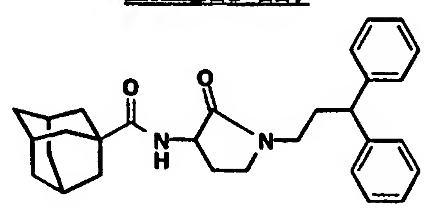
Example 225



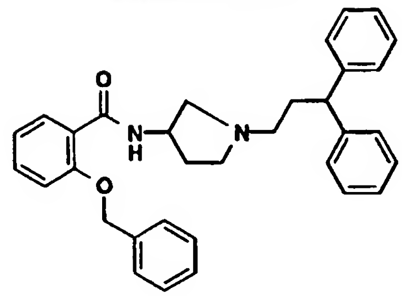
Example 226



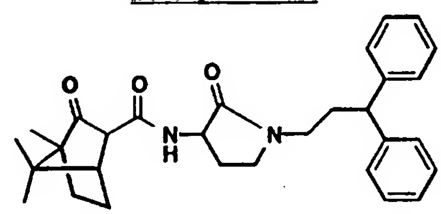
Example 227



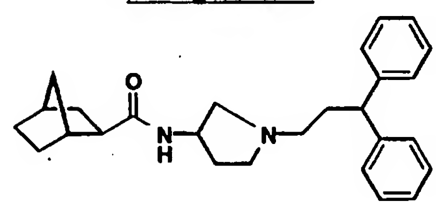
Example 228



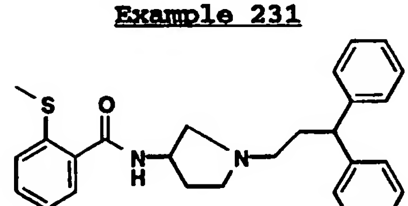
Example 229



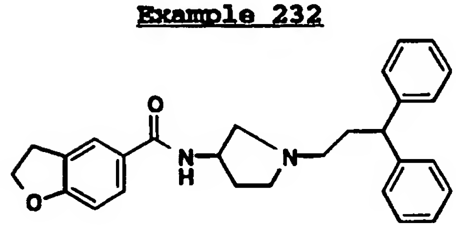
Example 230



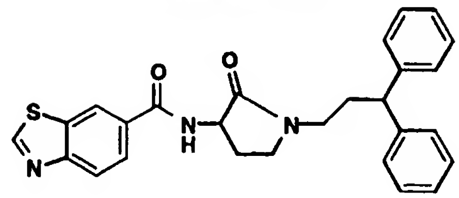
Example 231



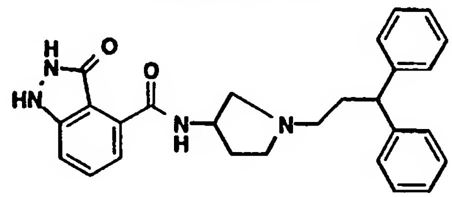
Example 232



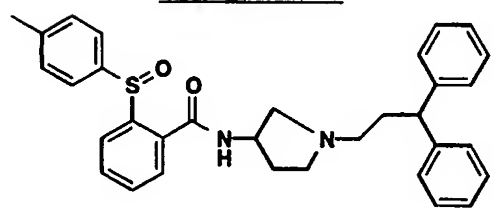
Example 233



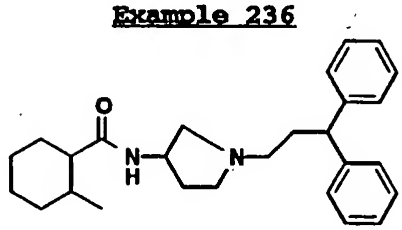
Example 234



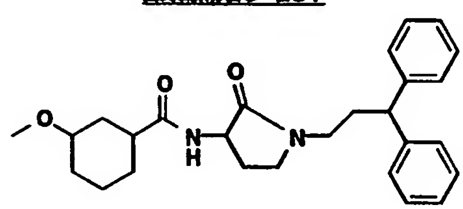
Example 235



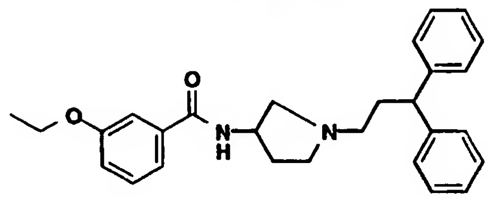
Example 236



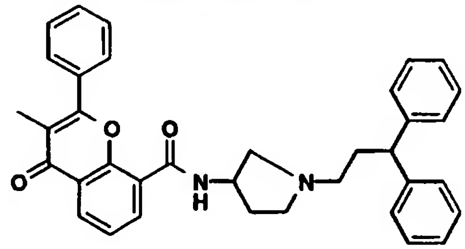
Example 237



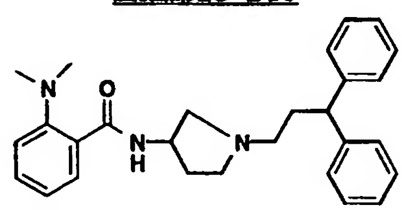
**Example 238**



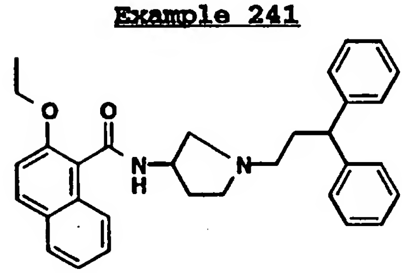
**Example 239**



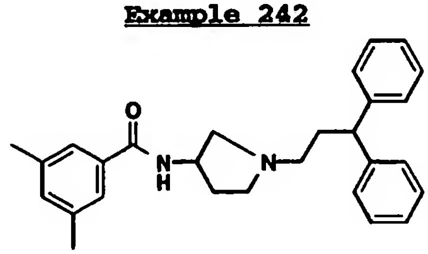
**Example 240**



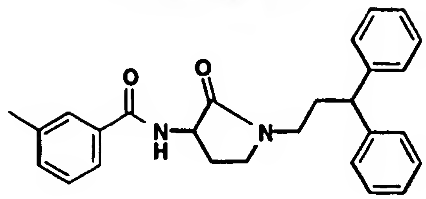
**Example 241**



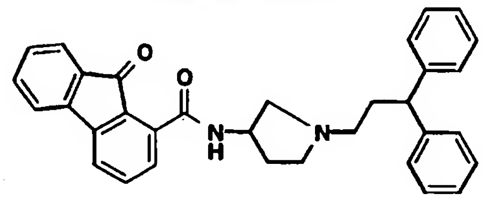
**Example 242**



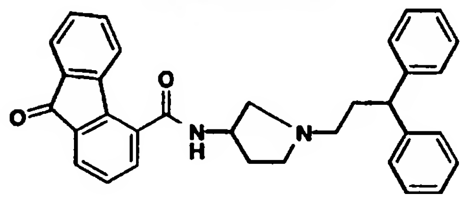
**Example 243**



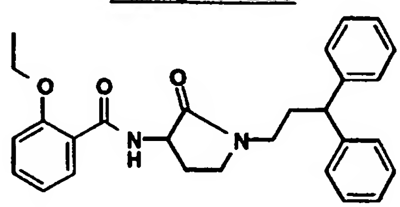
**Example 244**



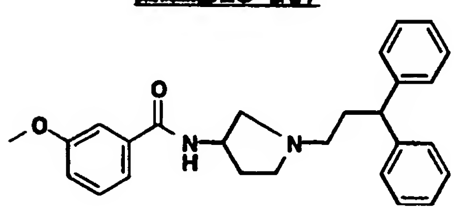
**Example 245**



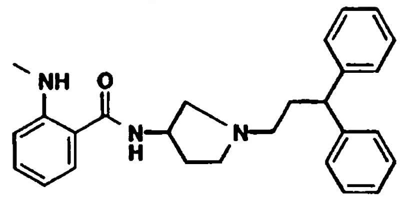
**Example 246**



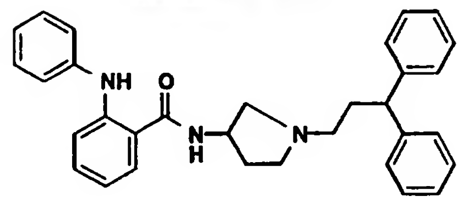
**Example 247**



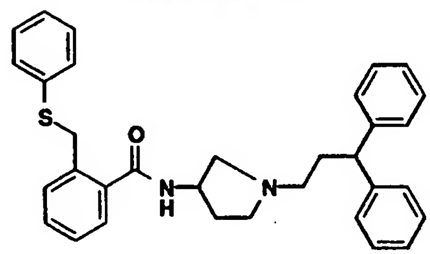
Example 248



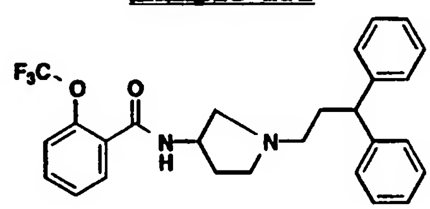

Example 249



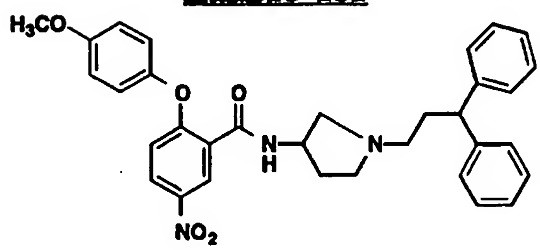

Example 250



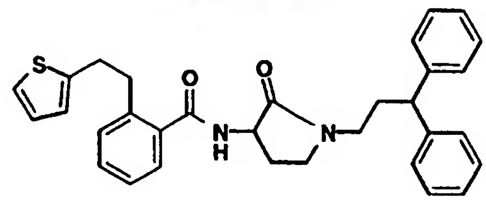

Example 251



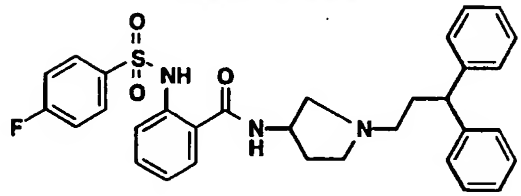

Example 252



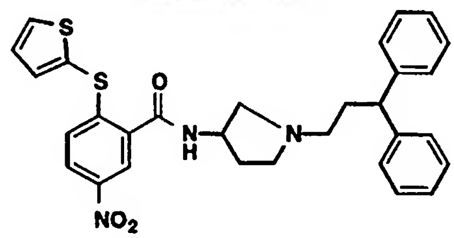
Example 253



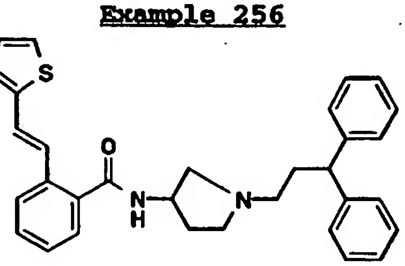
Example 254



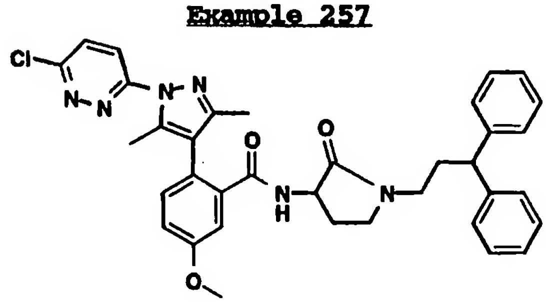
Example 255



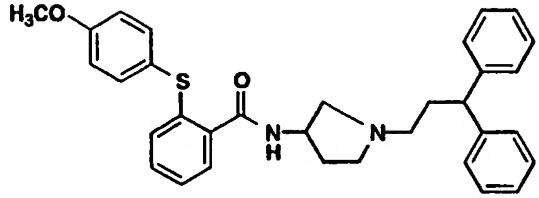
Example 256



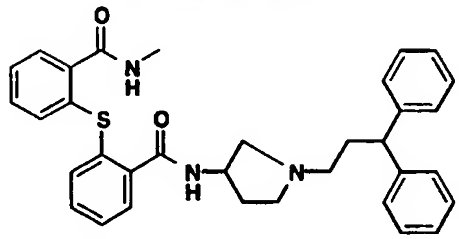
Example 257



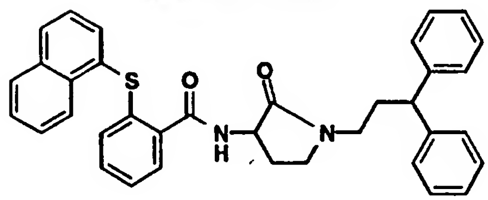
Example 258



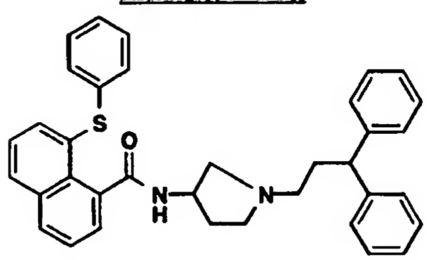

Example 259



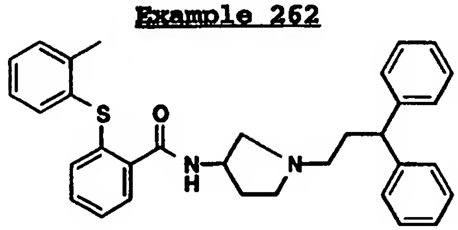

Example 260



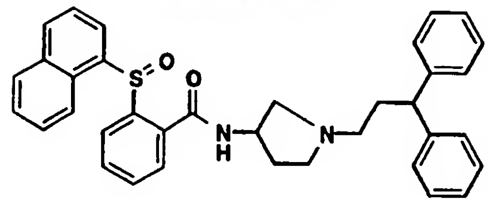

Example 261



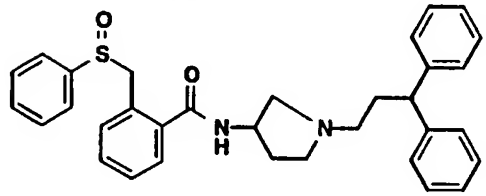

Example 262



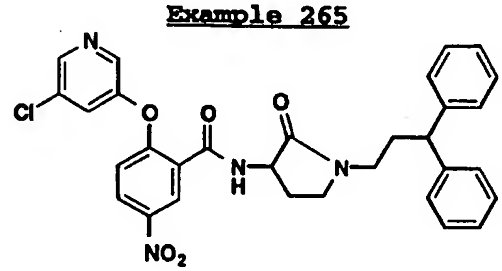
**Example 263**



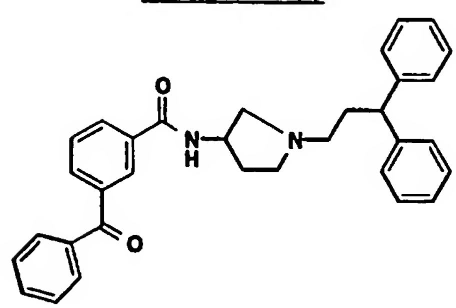
**Example 264**



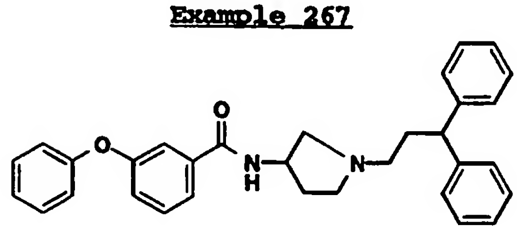
**Example 265**



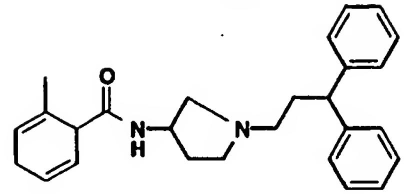
**Example 266**



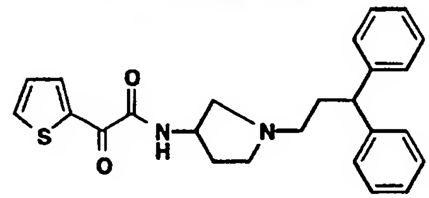
**Example 267**



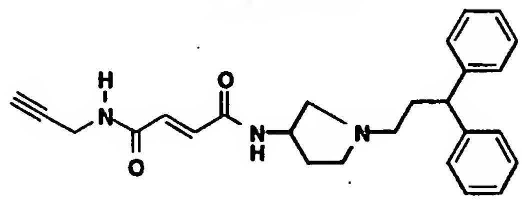
Example 268



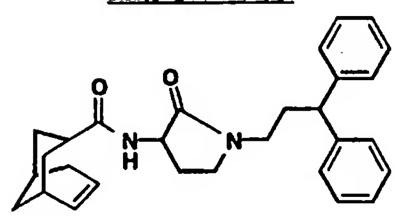

Example 269



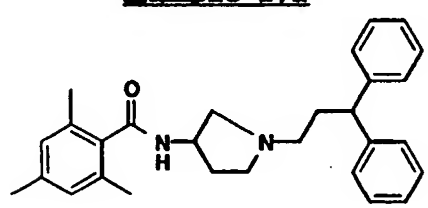

Example 270



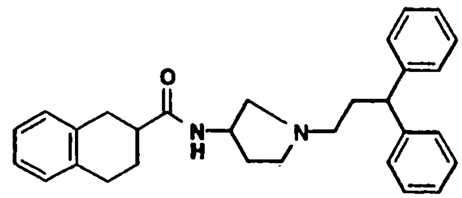

Example 271



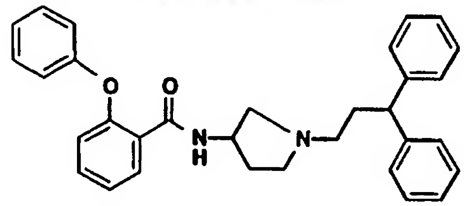

Example 272



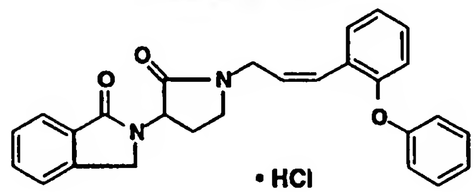
Example 273



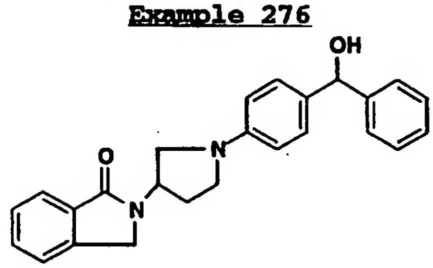
Example 274



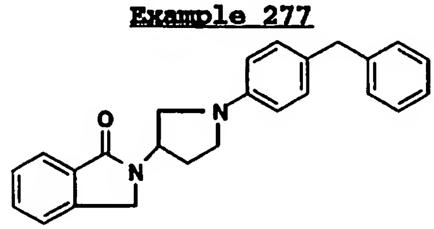
Example 275



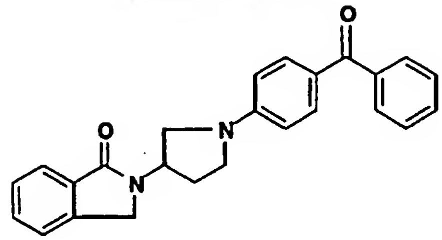
Example 276



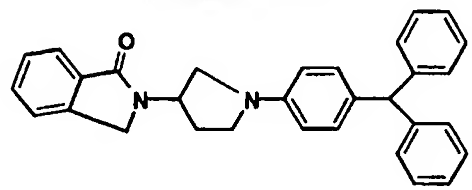
Example 277



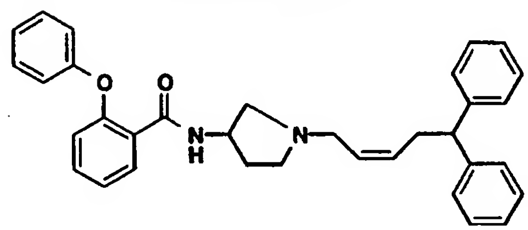
**Example 278**



**Example 279**



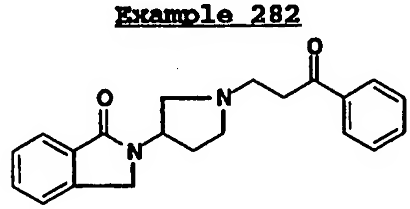
**Example 280**



**Example 281**

(Z)-N-[1-(5,5-Diphenyl-2-pentenyl)-3-pyrrolidinyl]-2-phenoxybenzamide

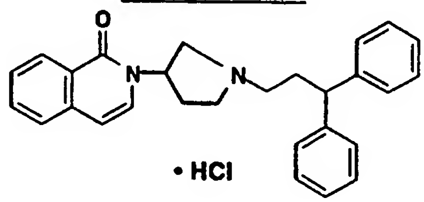
**Example 282**



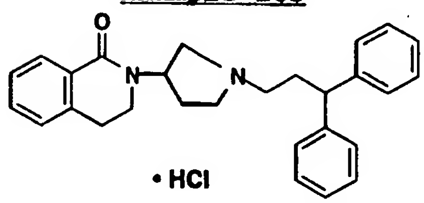
## Example 283

2,3-Dihydro-2-[1-[3-phenyl-3-(4-propylphenyl)-propyl]-3-pyrrolidinyl]-1H-isoindol-1-one, monohydrochloride

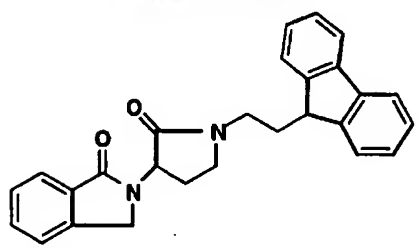
## Example 284



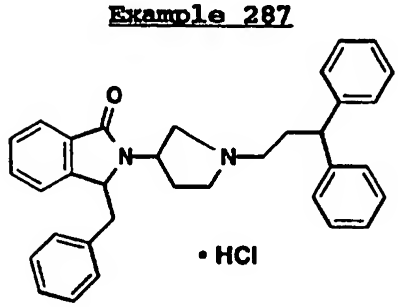
## Example 285



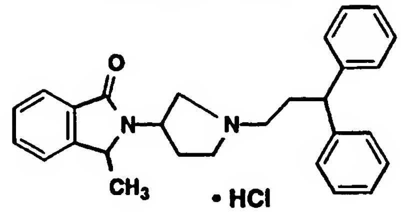
## Example 286



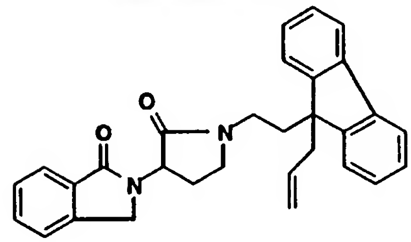
## Example 287



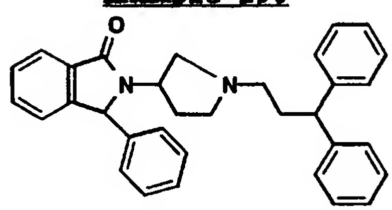
Example 288



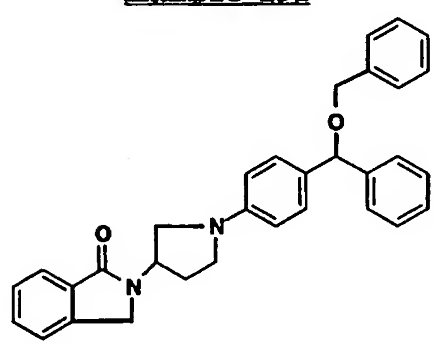
Example 289



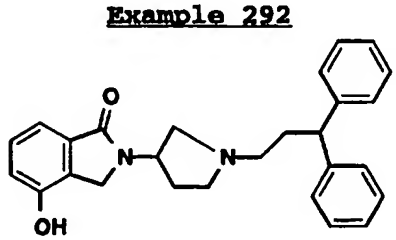
Example 290



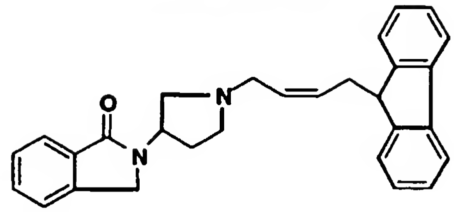
Example 291



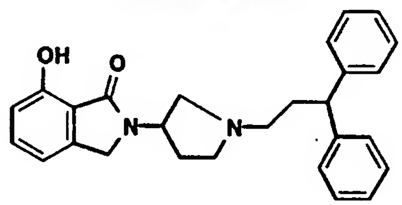
Example 292



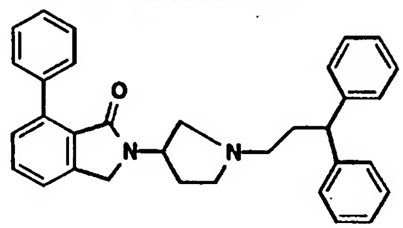
Example 293



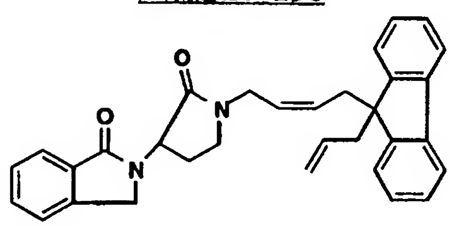
Example 294



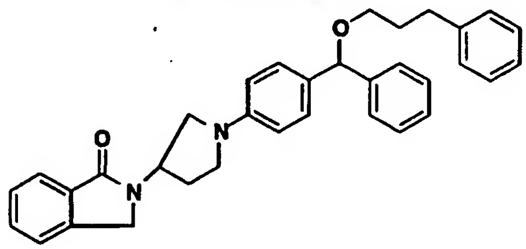
Example 295



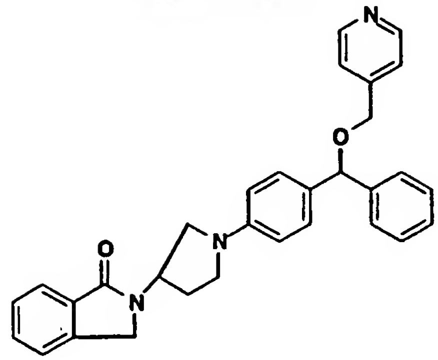
Example 296



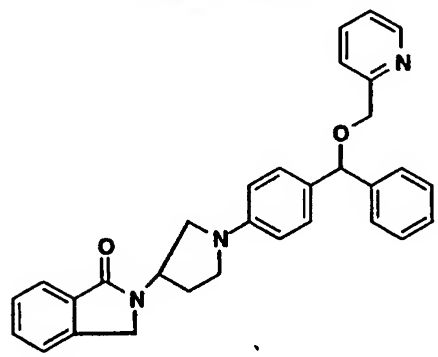
Example 297



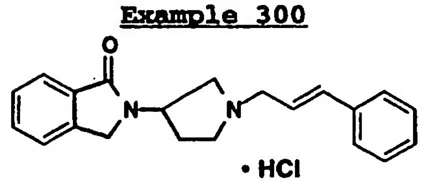
Example 298



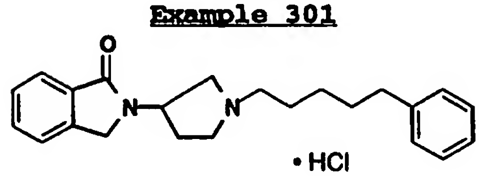
Example 299



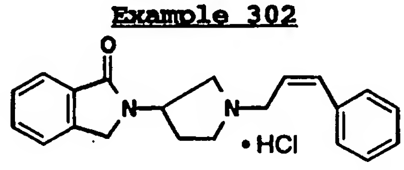
Example 300



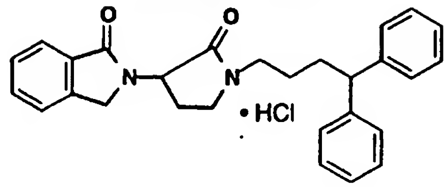
Example 301



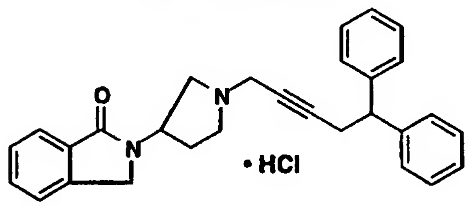
Example 302



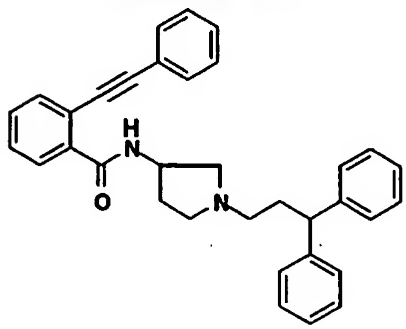
## Example 303



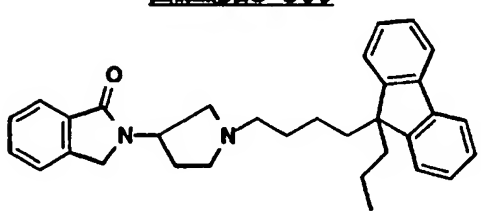
## Example 304



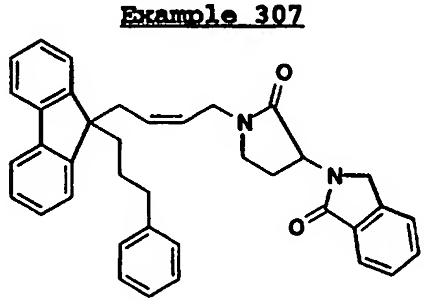
## Example 305



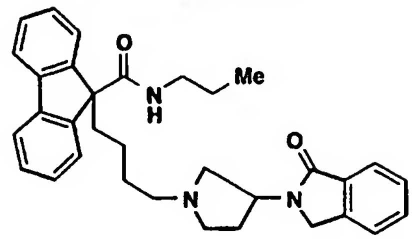
## Example 306



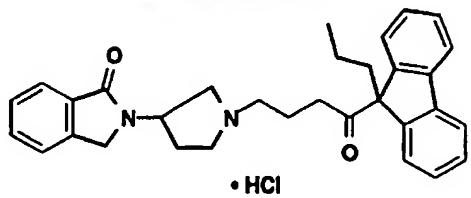
## Example 307



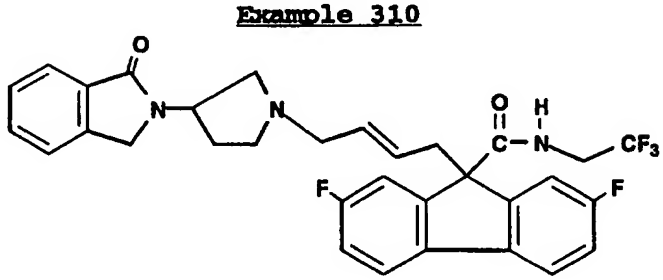
Example 308



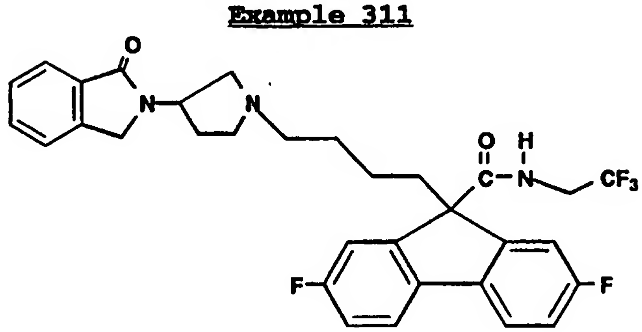
Example 309



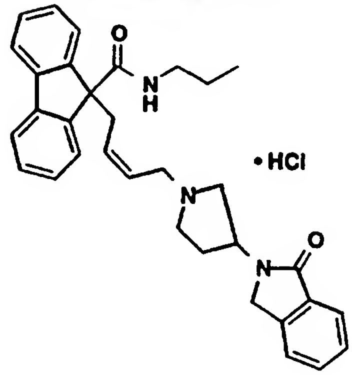
Example 310



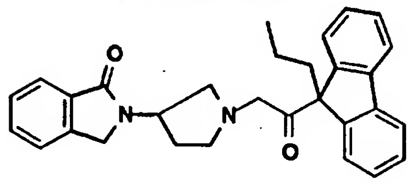
Example 311



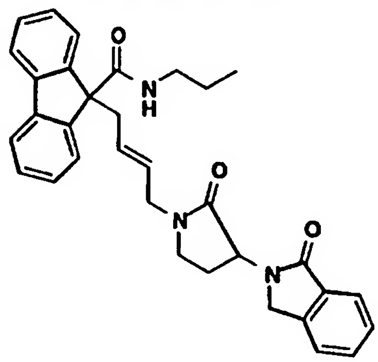
Example 312



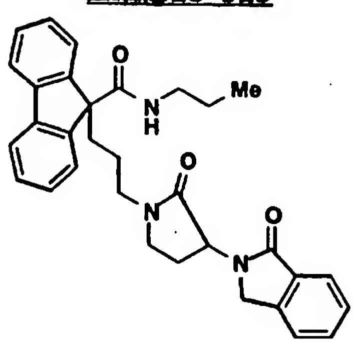

Example 313



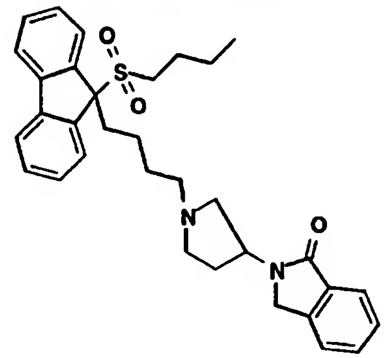

Example 314



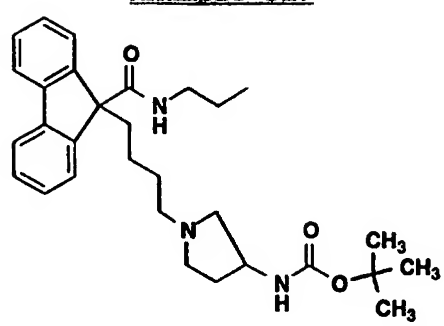

Example 315



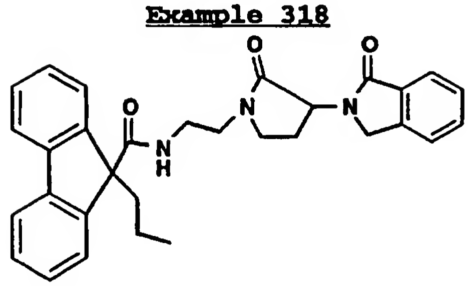
Example 316



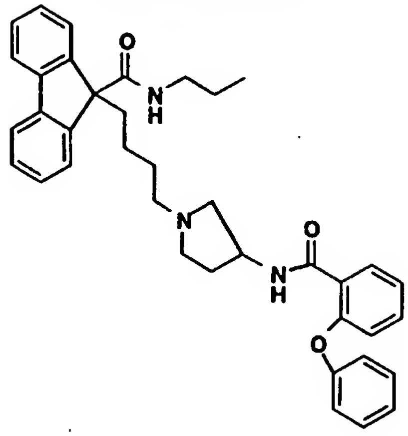
Example 317



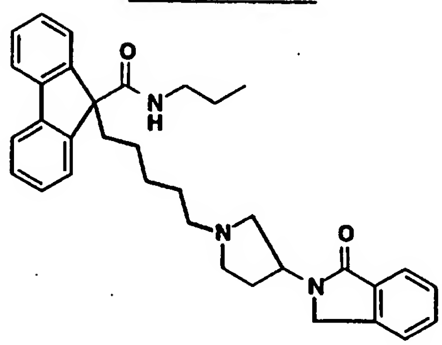
Example 318



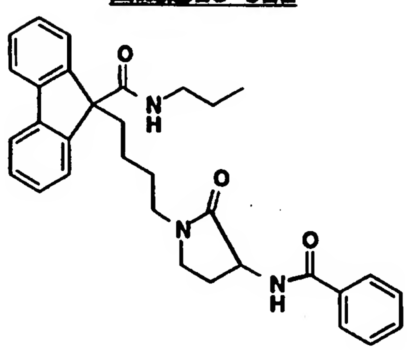
**Example 319**



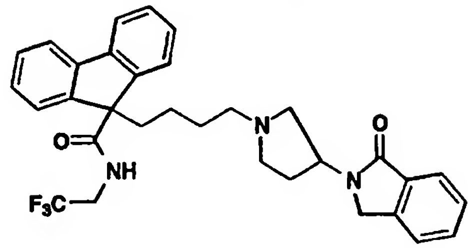
**Example 320**



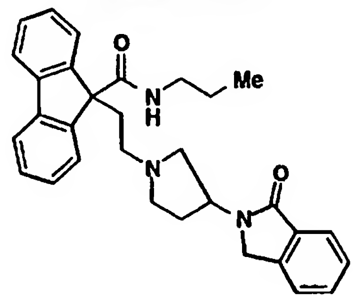
**Example 321**



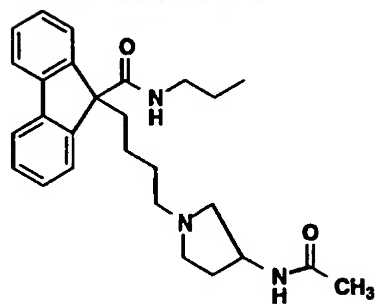
**Example 322**



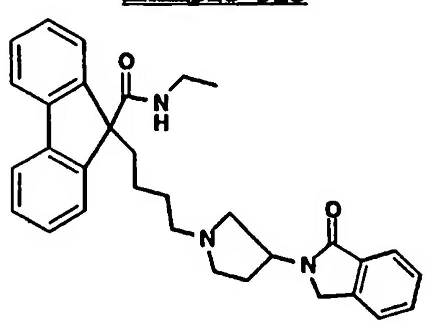
**Example 323**



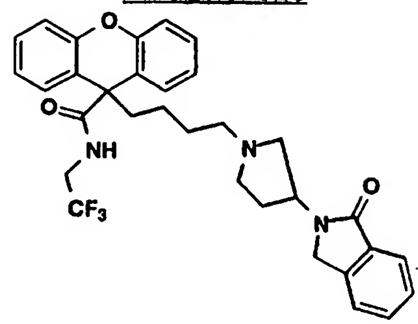
**Example 324**



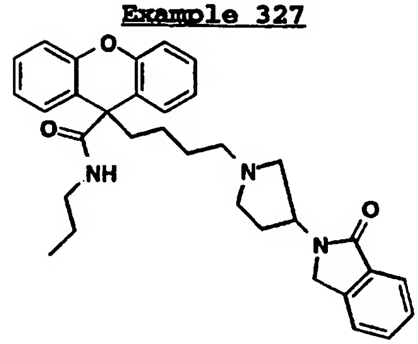
**Example 325**



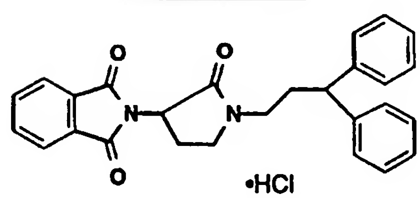
Example 326



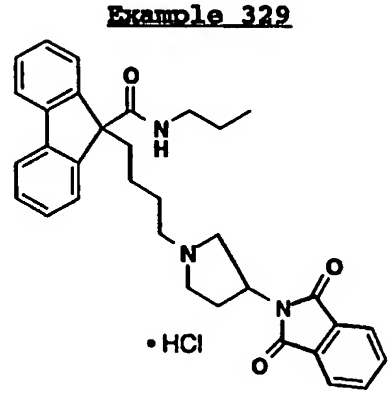
Example 327



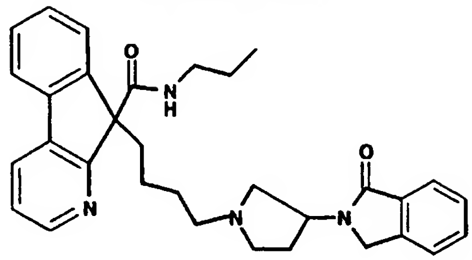
Example 328



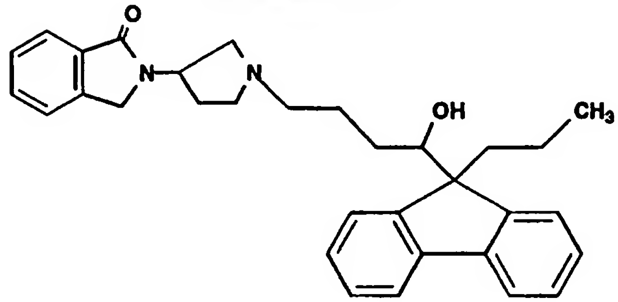
Example 329



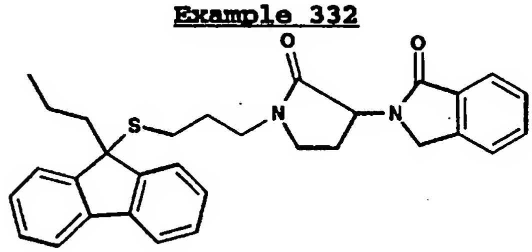
Example 330



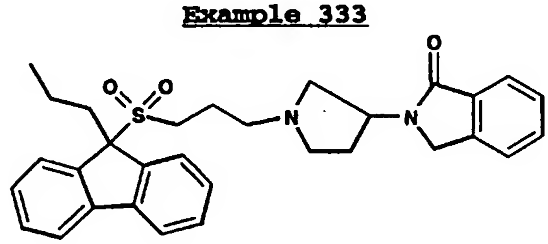
Example 331



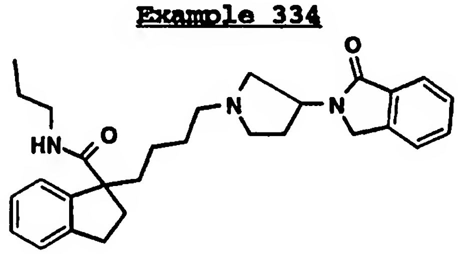
Example 332



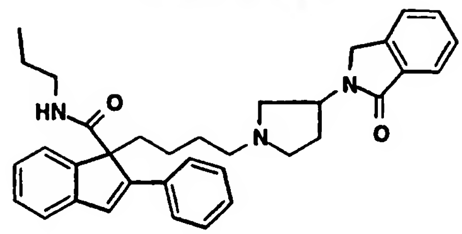
Example 333



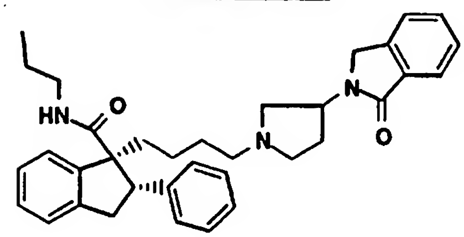
Example 334



Example 335

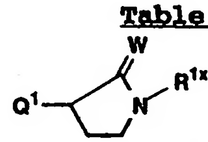


Example 336



Additional compounds falling within the scope of the present invention are described by the following structures. Substituents for each example are identified in the table following each structure.

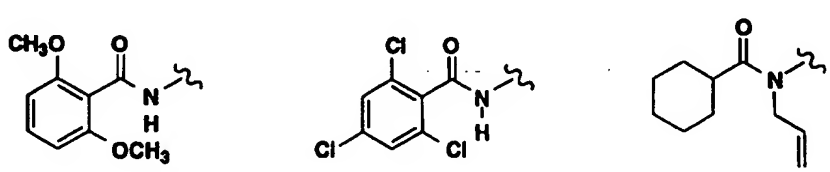
Table B



(Where W is H, H or O)

where $R^{1x}$ is (a), (b), (c), (d) or (e) as in Table A

| Examples of $Q^1$ |
|---|



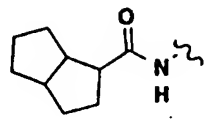
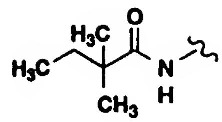
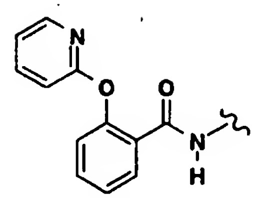
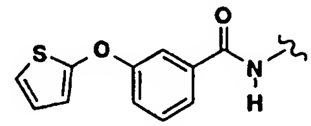
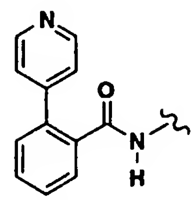
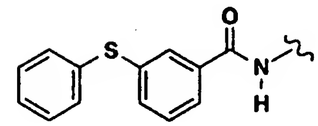
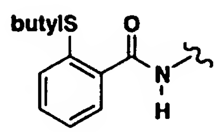
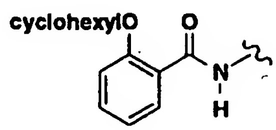
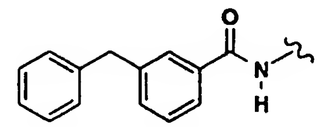
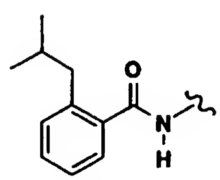
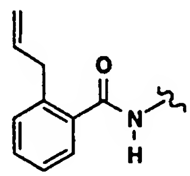
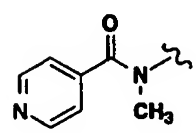
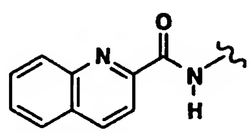
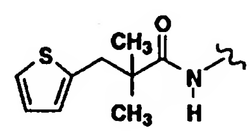
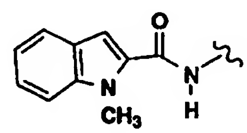
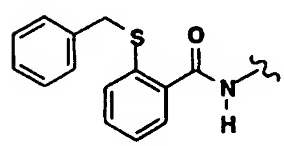
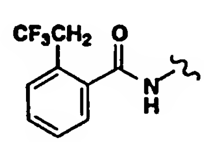
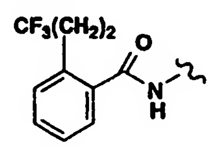
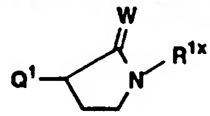
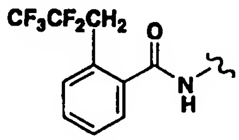
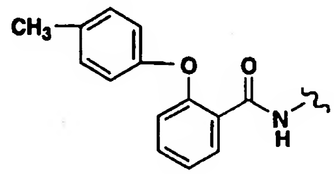
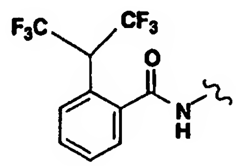
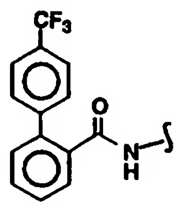
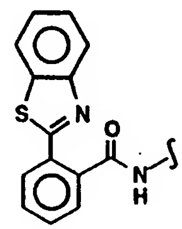
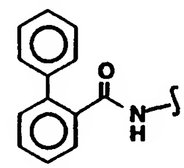
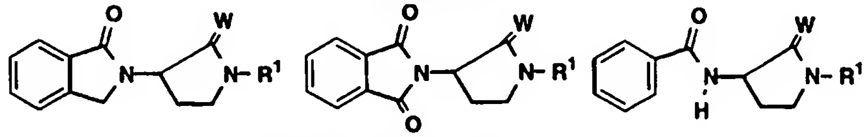



















**Table B (continued)**



| Examples of $Q^1$ | | |
|---|---|---|
|  |  |  |
|  |  |  |

## Table C




(Where W is H, H or O)

**Examples of $R^1$**

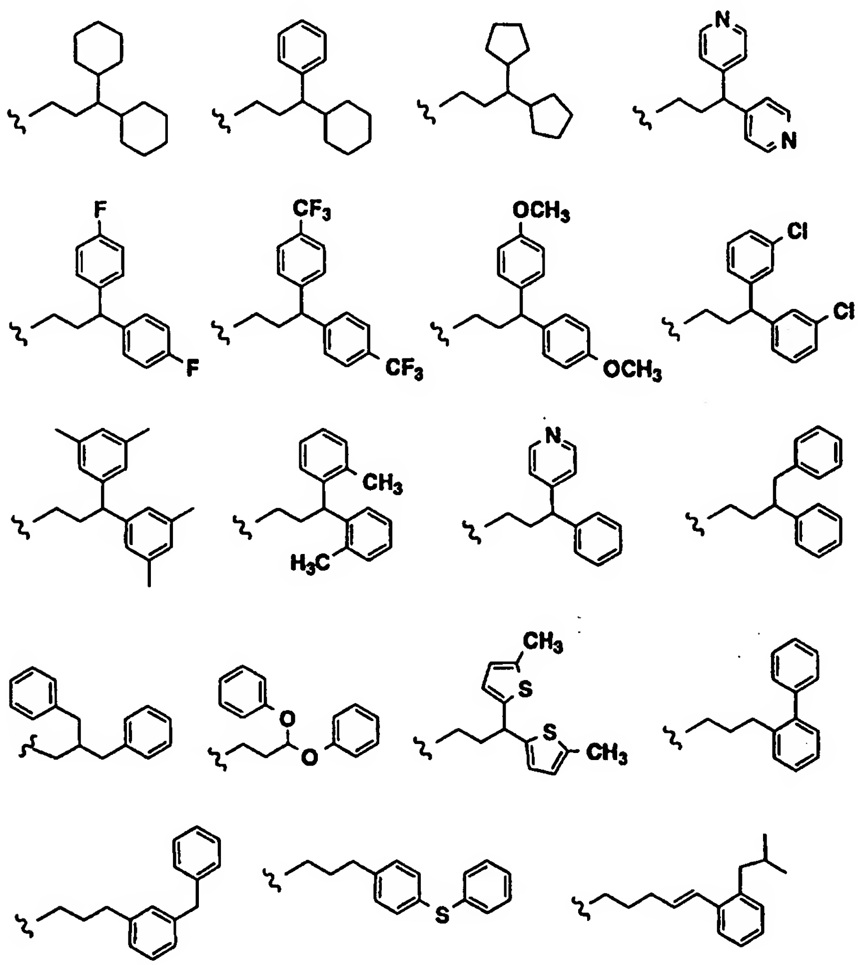
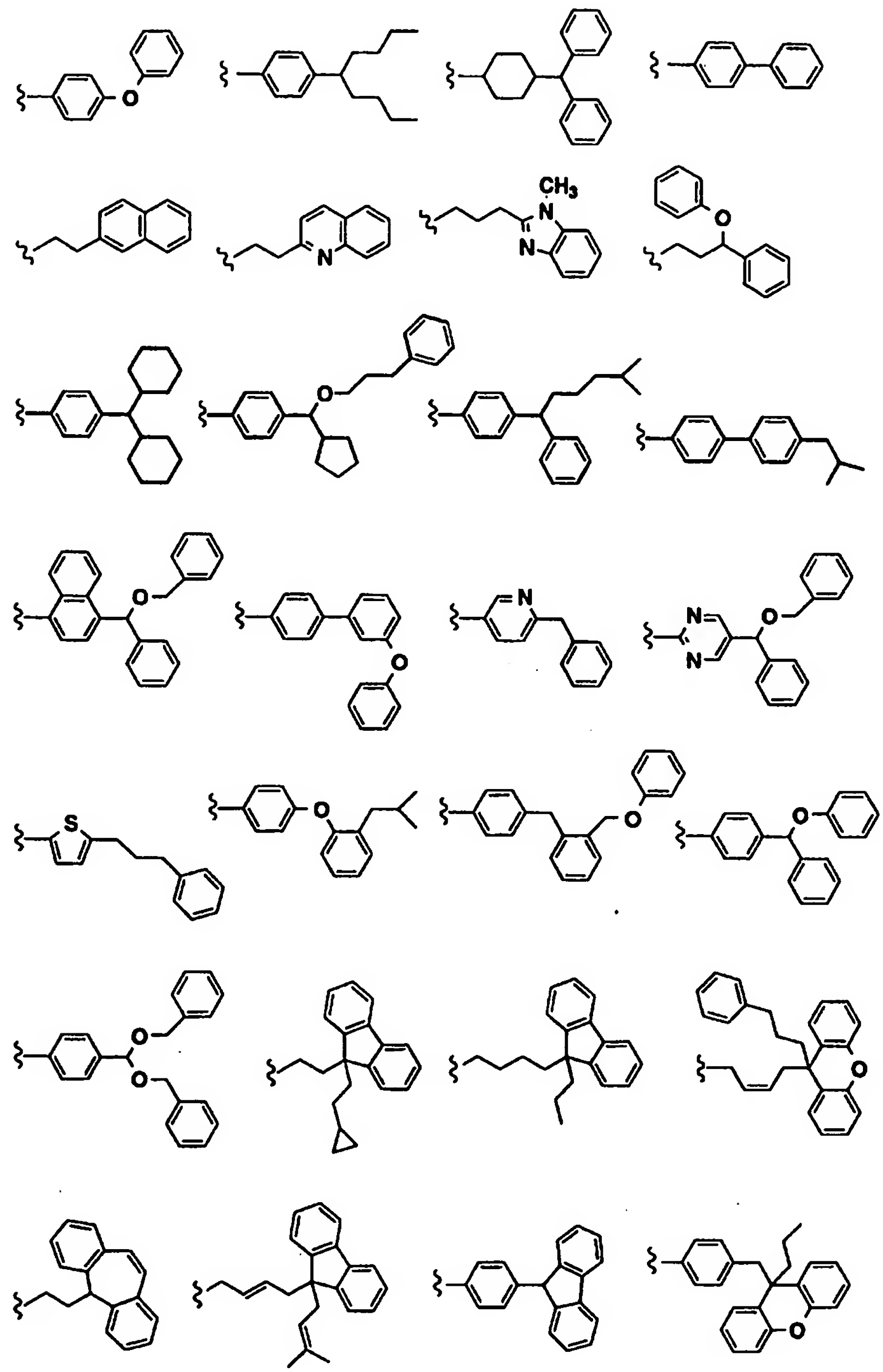
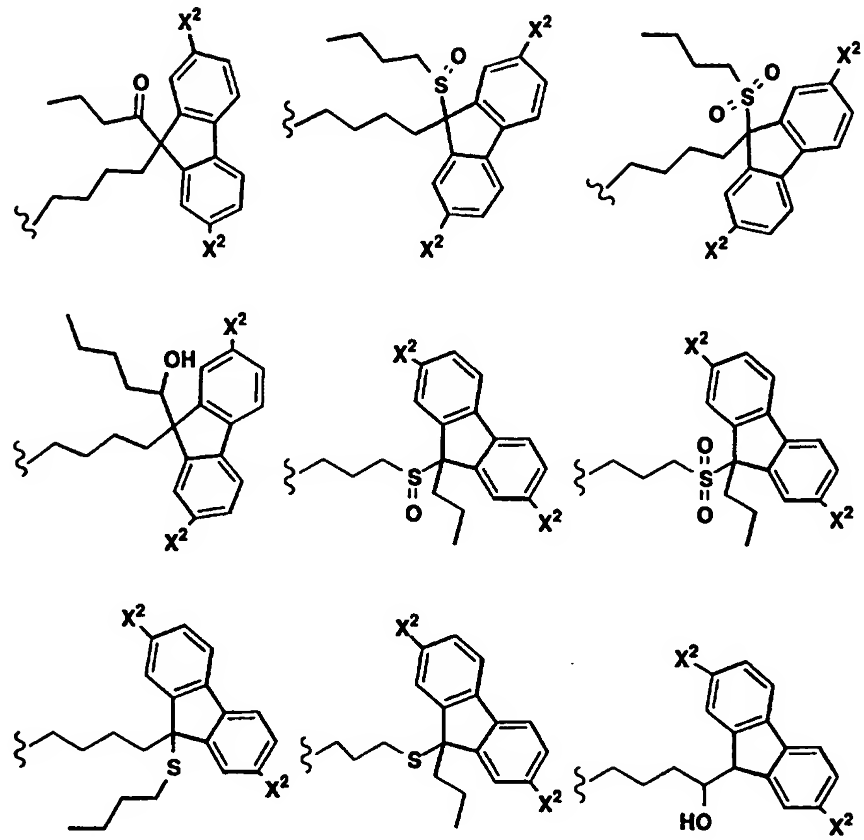
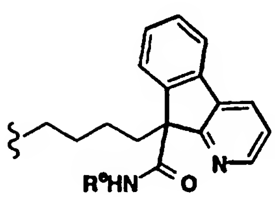


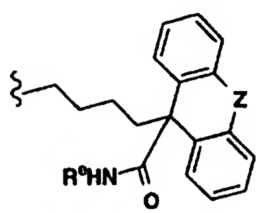
**Table C (continued)**







$R^e$=propyl, $CF_3CH_2$-

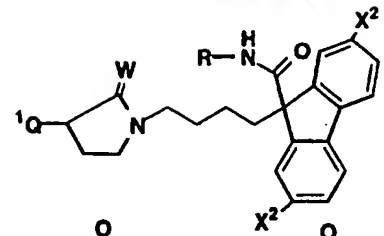


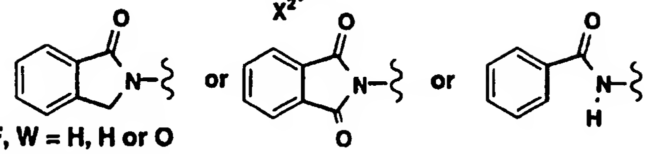
Z=O,S

$R^e$=propyl, $CF_3CH_2$-

$X^2$ for Table C = H or F

## Table D



$Q^1 =$ 

$X^2$ = H or F, W = H, H or O

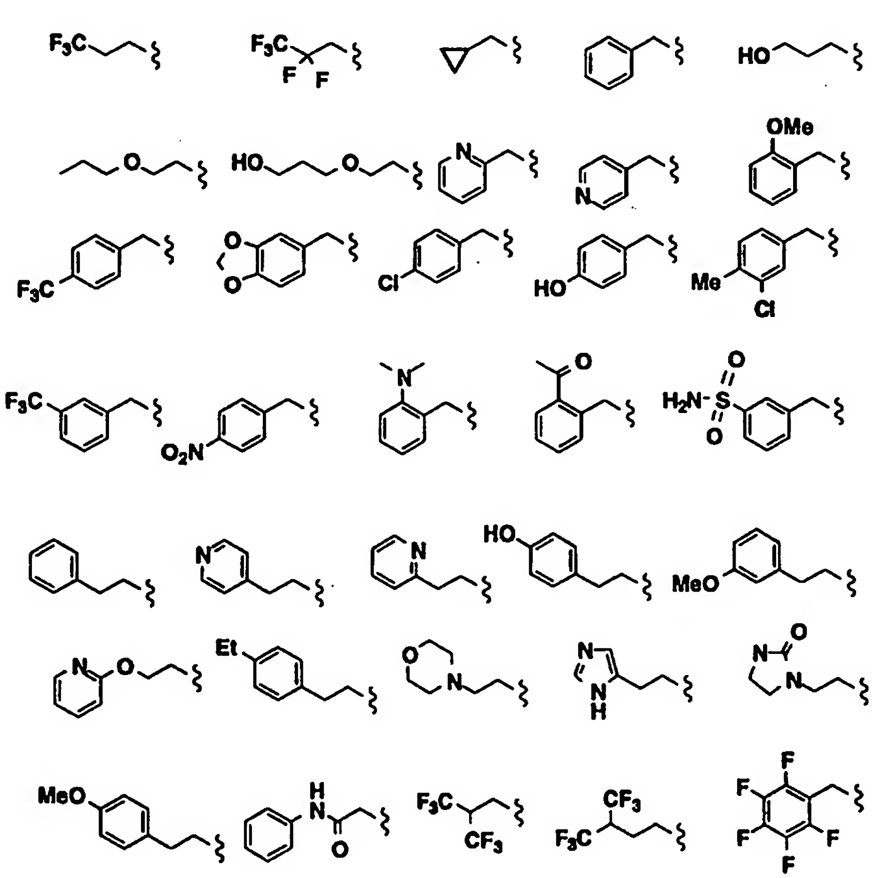
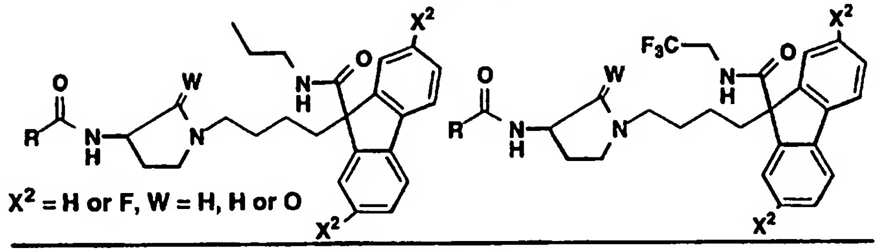
| Example of R |
|---|
|  |

Table E




Example of R

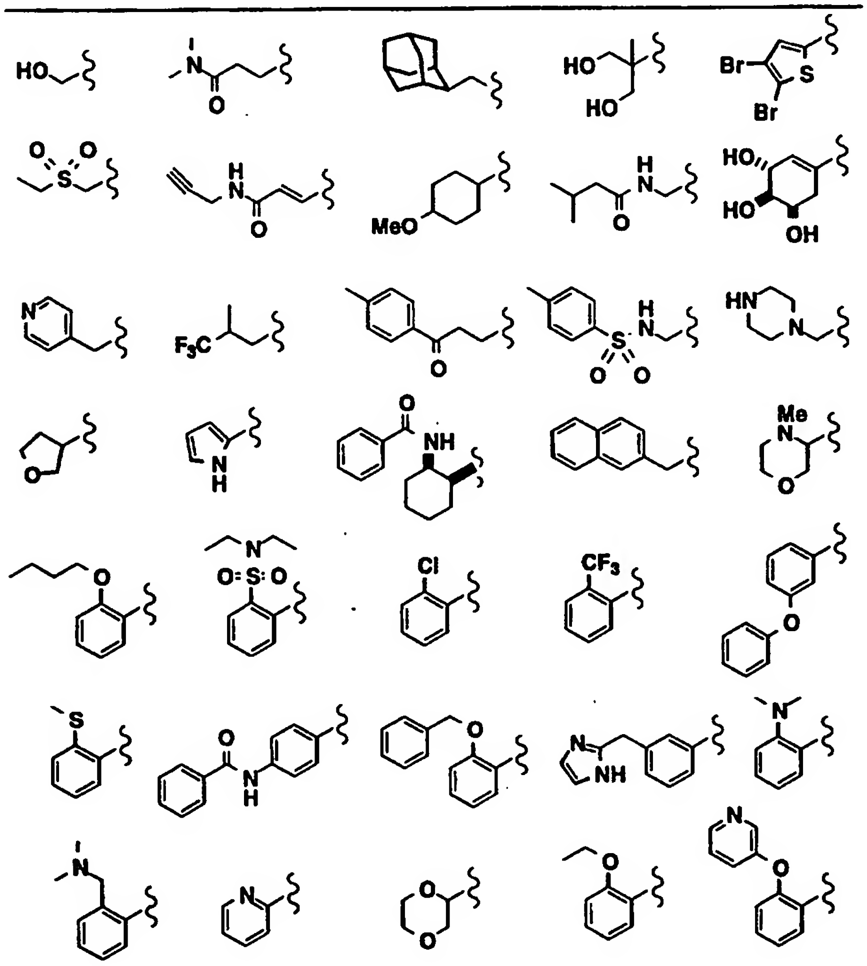
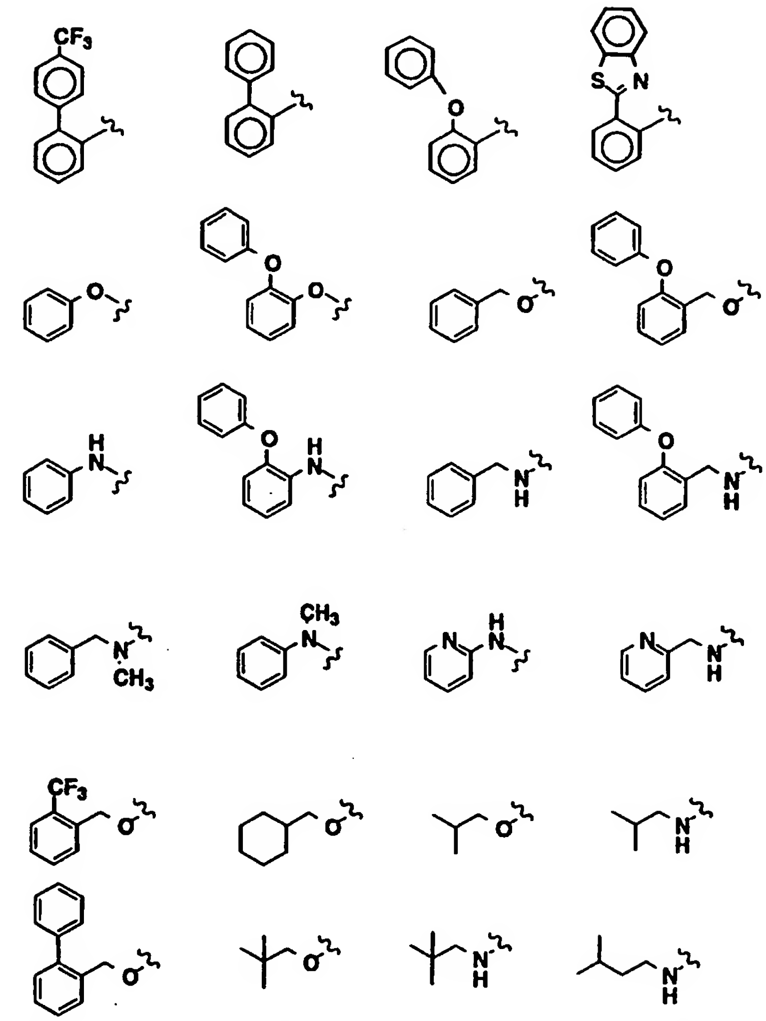
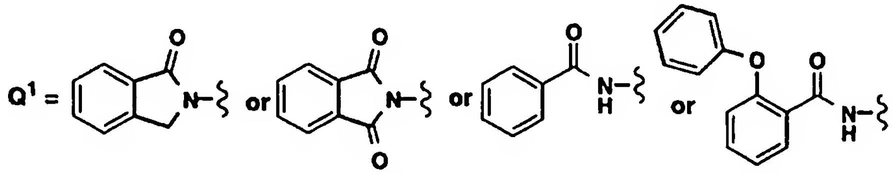


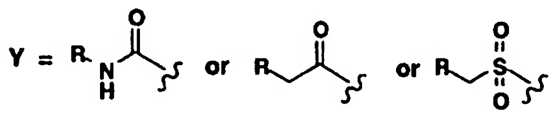
**Table E (Cont'd)**



<u>Table F</u>

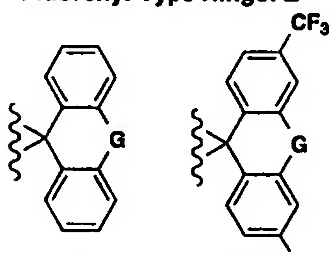

W is H, H or O



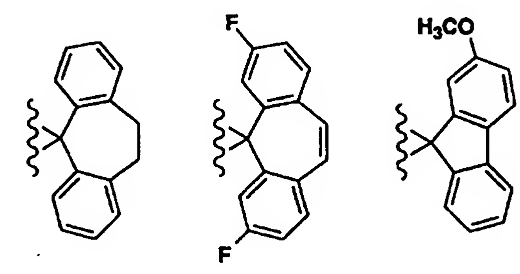


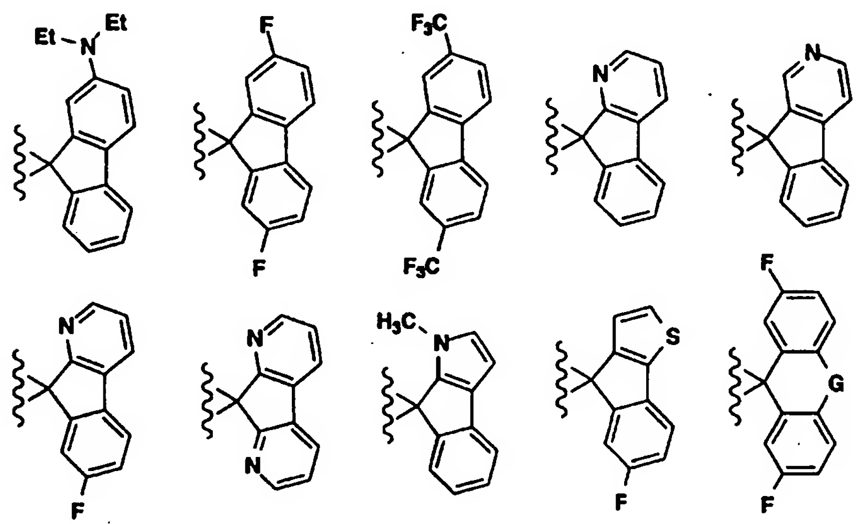
R = propyl or $CF_3CH_2$

Fluorenyl-Type Rings: Z =



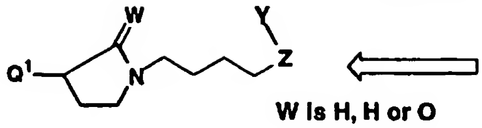
G = $CH_2$, O, S, SO, $SO_2$





G = $CH_2$, O, S, SO, $SO_2$

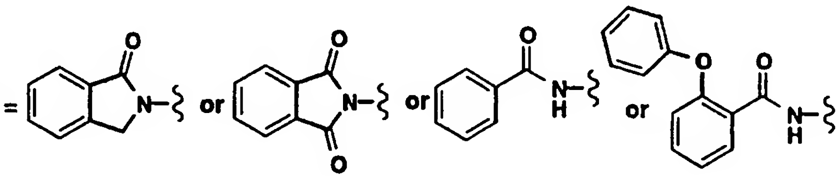
## Table G



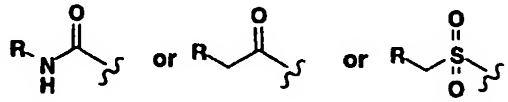

Indenyl-Type Compounds

W is H, H or O

$Q^1$ =




Y =




R = propyl or $CF_3CH_2$

Indenyl-Type Rings: Z =

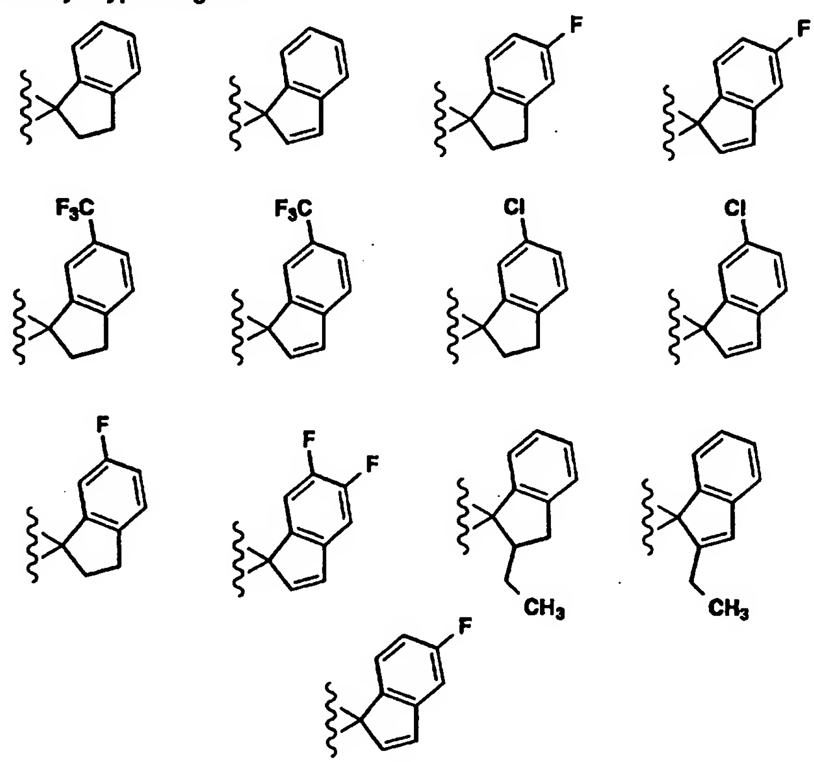


Table G (cont'd)

Indenyl-Type Rings: Z =

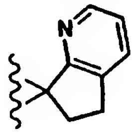
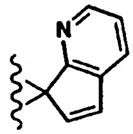
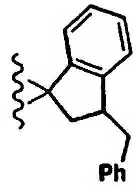
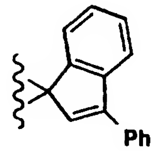
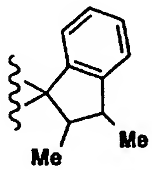
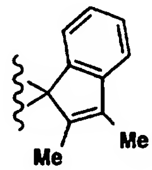
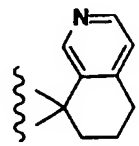
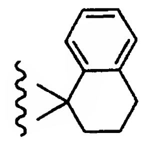
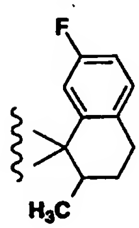
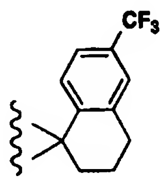
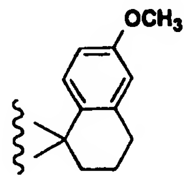
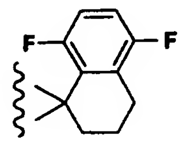
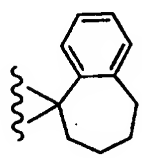
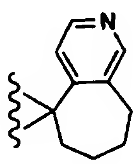
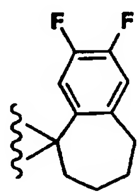
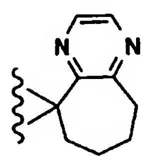
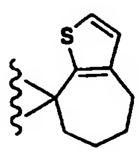
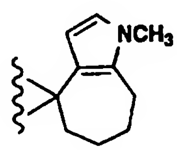
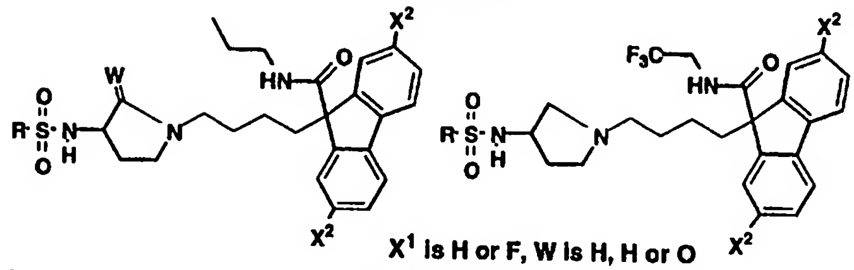
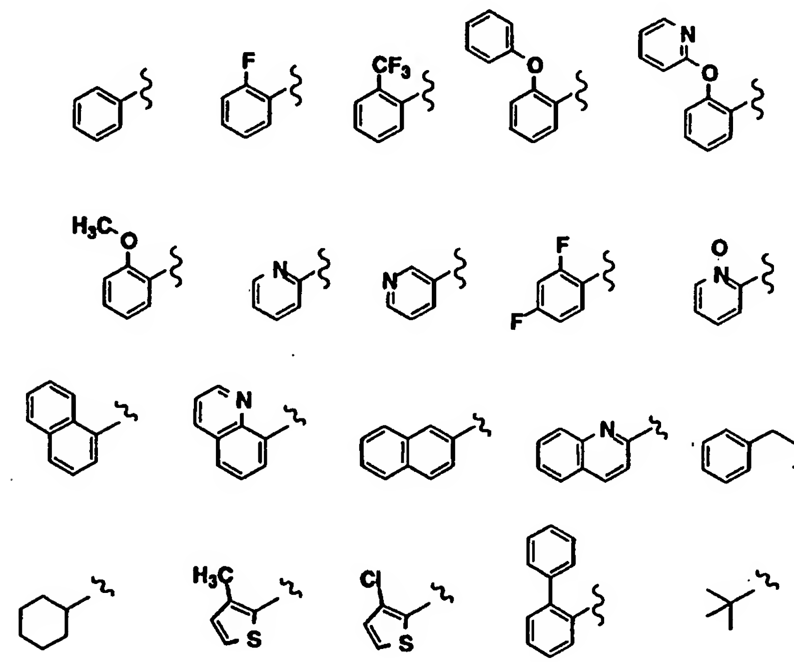



















**Table H**



$X^1$ is H or F, W is H, H or O

**Example of R**



**Example 337**

cis-9-[4-[3-(2,3-Dihydro-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, N-oxide

**Example 338**

2-[1-[4-[9-(Butylsulfonyl)-9H-fluoren-9-yl]butyl]-3-pyrrolidinyl]-2,3-dihydro-1H-isoindol-1-one

**Example 339**

9-[4-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-1-pyrrolidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

**Example 340**

9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

**Example 341**

9-[4-[[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

**Example 342**

9-[4-[[3-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

**Example 343**

2,7-Difluoro-9-[4-[[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

**Example 344**

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

**Example 345**

2,3-Dihydro-2-[1-[4-[9-(1-oxopentyl)-9H-fluoren-9-yl]butyl]-3-pyrrolidinyl]-1H-isoindol-1-one, monohydrochloride

**Example 346**

2,3-Dihydro-2-[1-(1-oxo-3,3-diphenylpropyl)-3-pyrrolidinyl]-1H-isoindol-1-one

**Example 347**

[1-[4-[9-[(Propylamino)carbonyl]-9H-fluoren-9-yl]-butyl]-3-pyrrolidinyl]carbamic acid, phenylmethyl ester, monohydrochloride

**Example 348**

9-[4-[3-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride salt

**Example 349**

9-[4-[3-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride salt

**Example 350**

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide

**Example 351**

9-[4-[3-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-pyrrolidinyl]-butyl]-N-propyl-9H-fluorene-9-carboxamide

## Example 352

9-[4-[3-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,3,3,4,4,4-heptafluorobutyl)-9H-fluorene-9-carboxamide, monohydrochloride

## Example 353

9-[4-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-1-pyrrolidinyl]butyl]-3,6-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

## Example 354

1-[4-[3-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-2-methyl-N-(2,2,2-trifluoroethyl)-1H-indene-1-carboxamide

## Example 355

9-[4-[3-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,3,3,3-pentafluoropropyl)-9H-fluorene-9-carboxamide, monohydrochloride

## Example 356

1-[4-[3-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-1H-indene-1-carboxamide

## Example 357

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-3,6-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

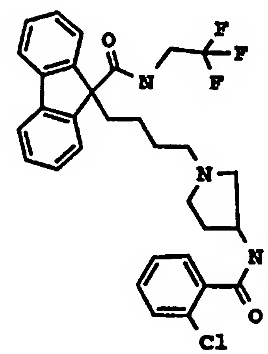
## Example 358

3,6-Difluoro-9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

Please note that in the Examples 359 to 477 for structures bearing only two single bonded substituents to nitrogen, the third substituent is always hydrogen, but it is not shown explicitly in the structures. Also, please note that in the Examples 359 to 475 for structures bearing oxygen and sulfurs with only one single bonded substituent, the second substituent is always hydrogen, but is not shown explicitly in the structures.

Example No.

359

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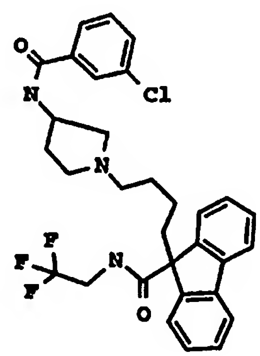

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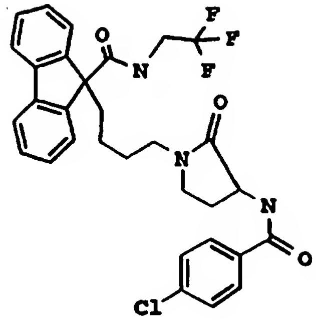

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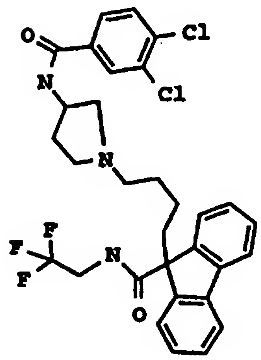

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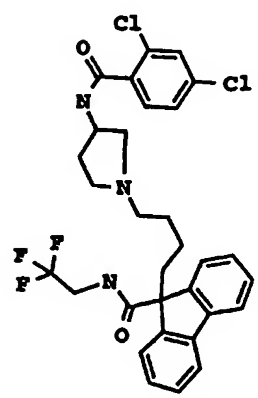

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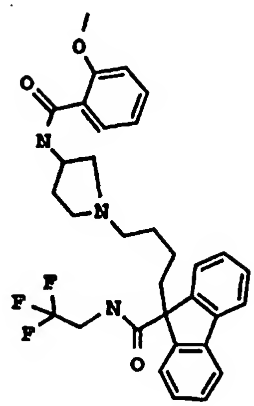


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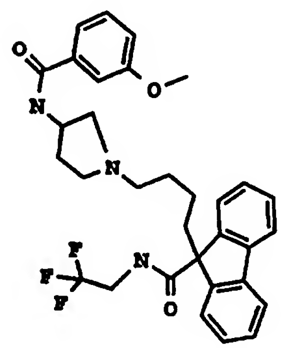


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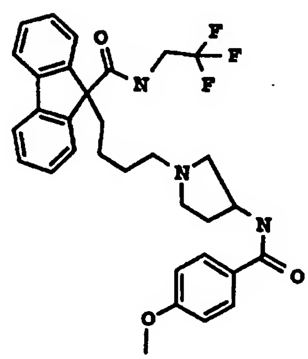


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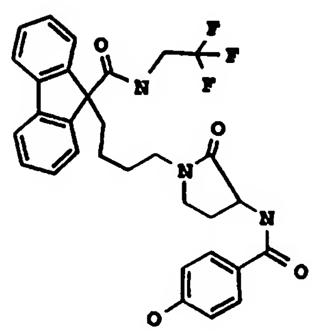
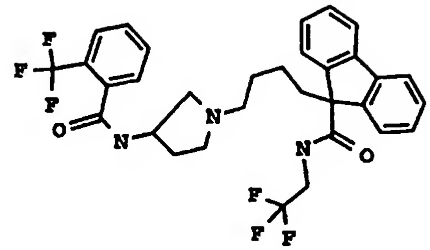
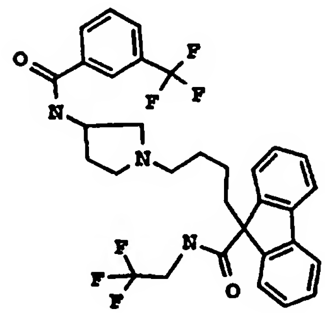
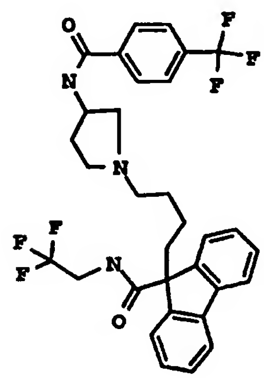
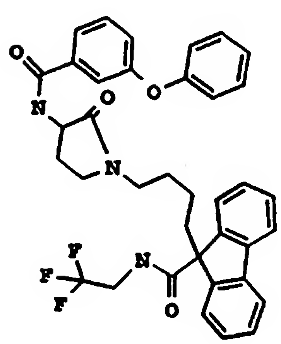


368 

369 

370 

371 

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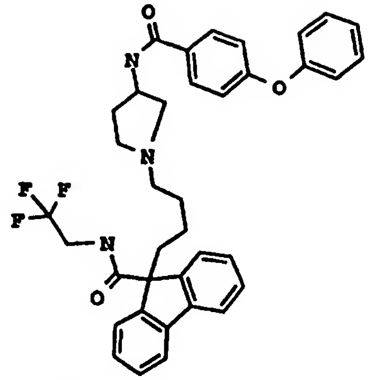

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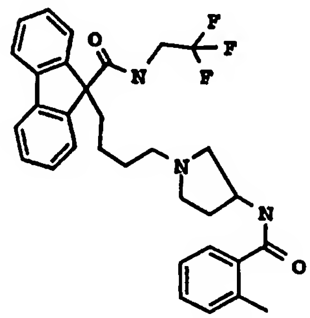

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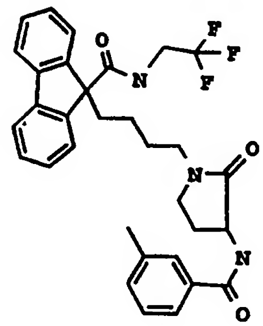

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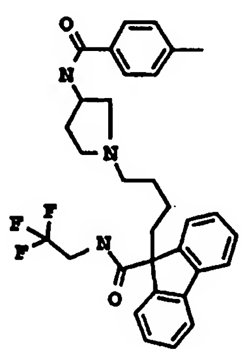

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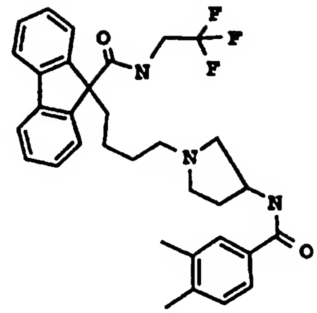


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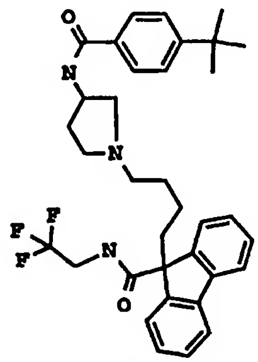


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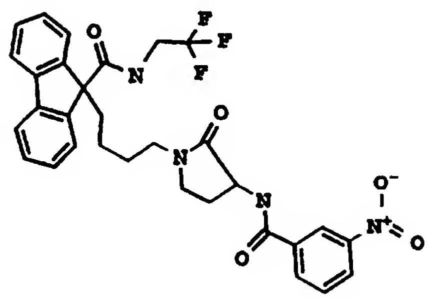


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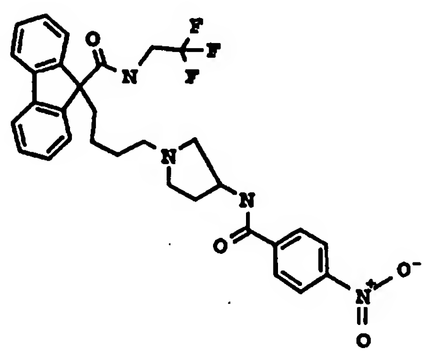
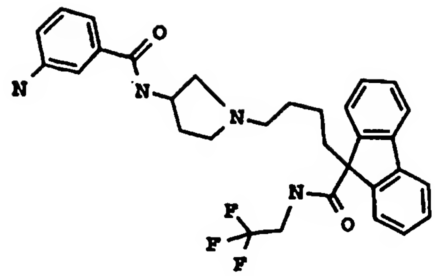
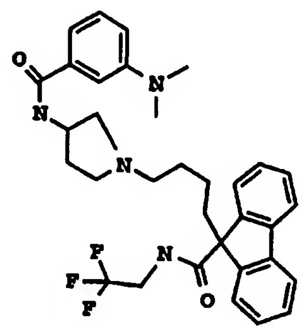
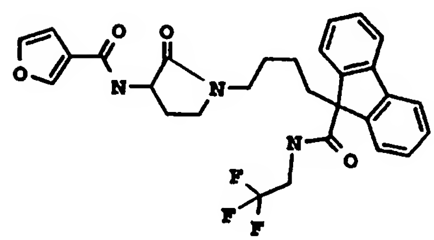
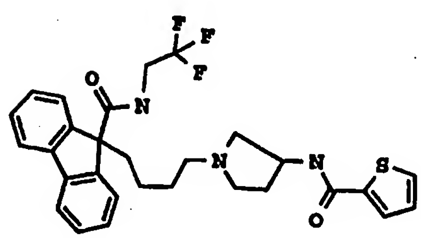


380 

381 

382 

383 

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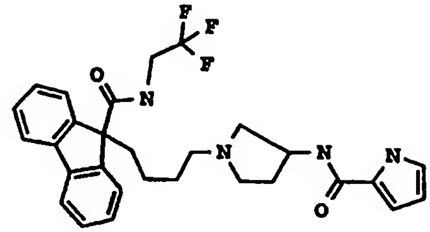

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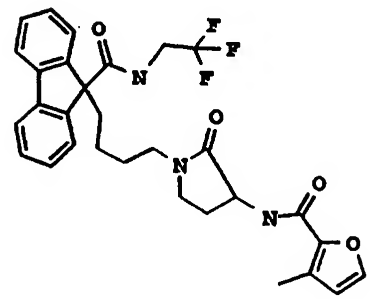

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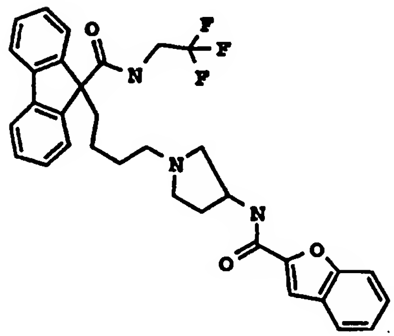

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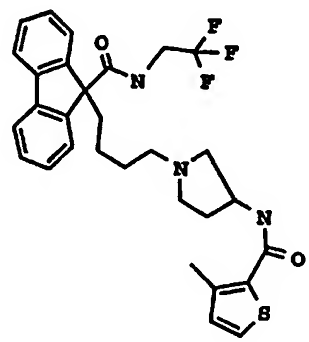
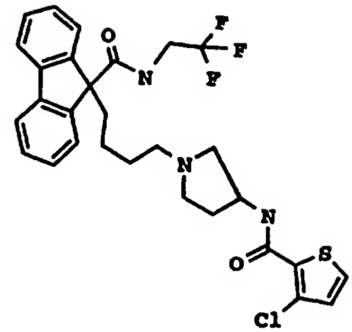
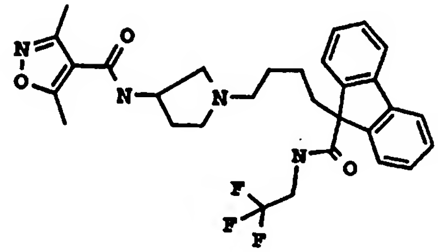
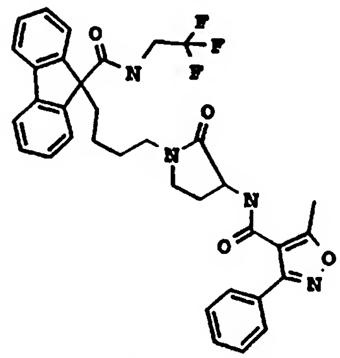
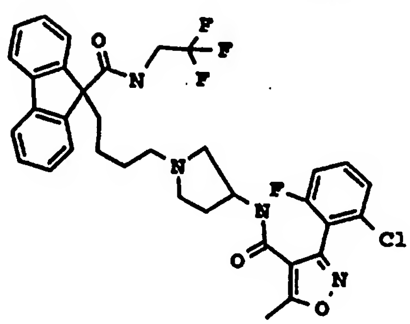


388 

389 

390 

391 

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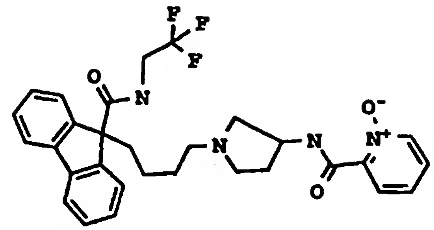


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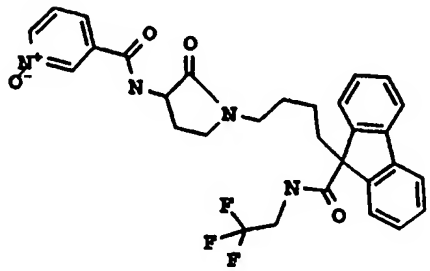


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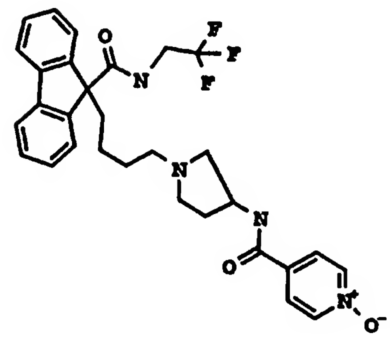


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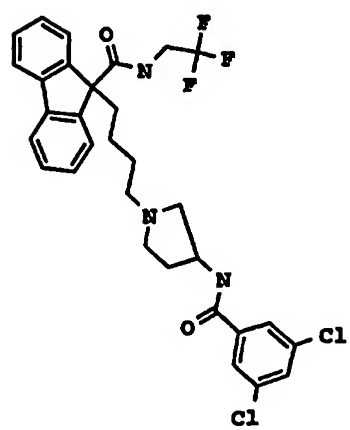
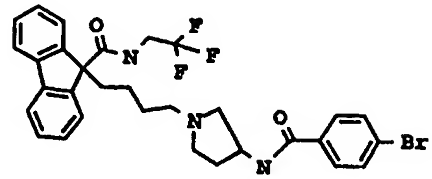
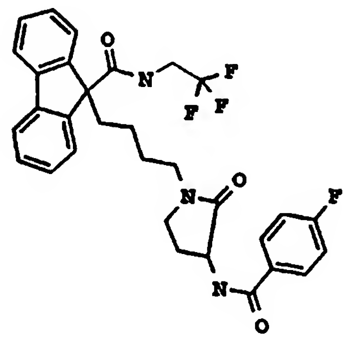
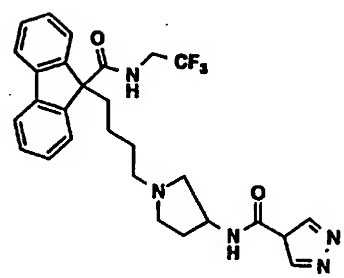
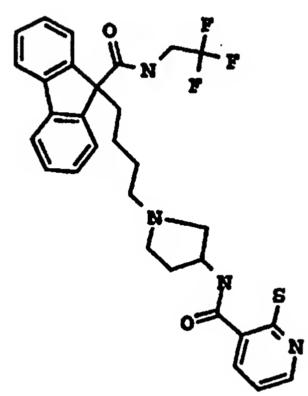
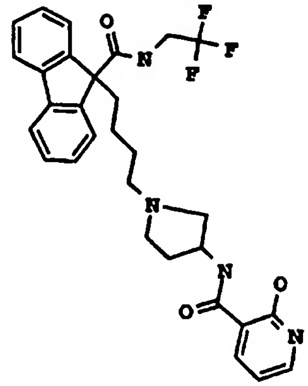


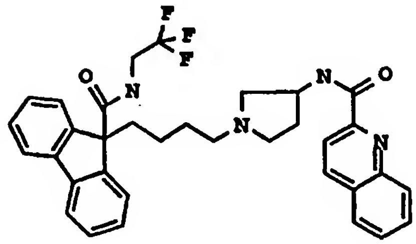
396 

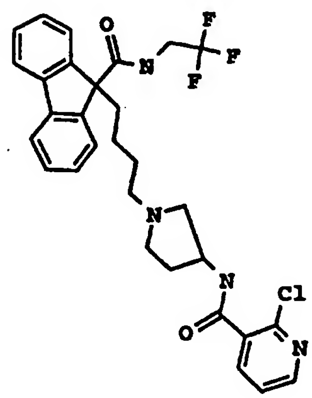
397 

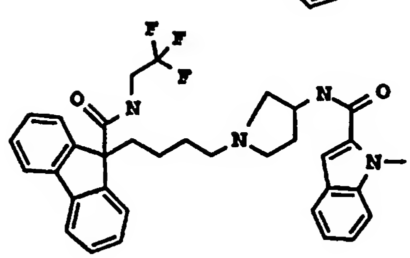
398 

399 

400 

401 

402 

403 

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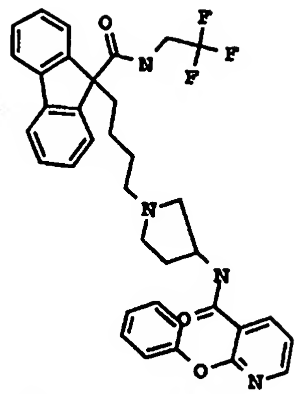

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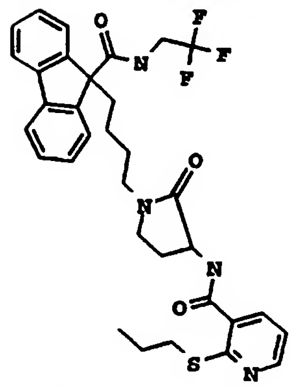

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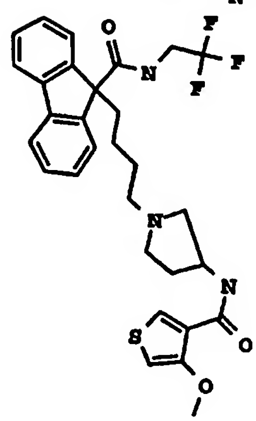

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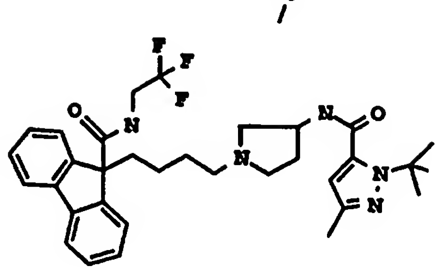
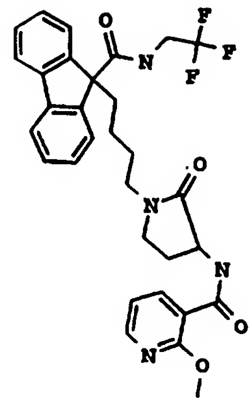
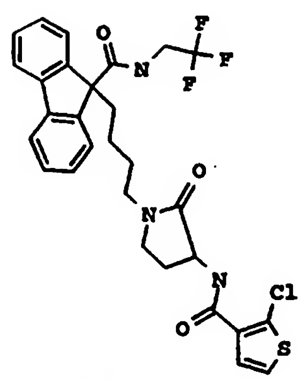
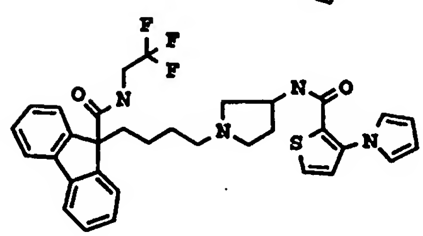
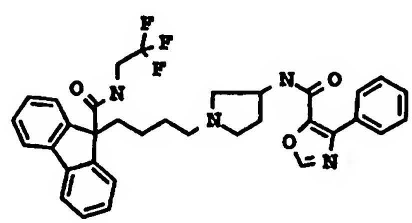


408 

409 

410 

411 

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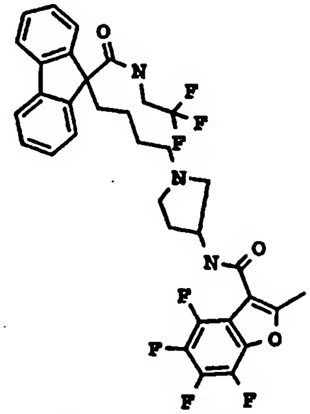

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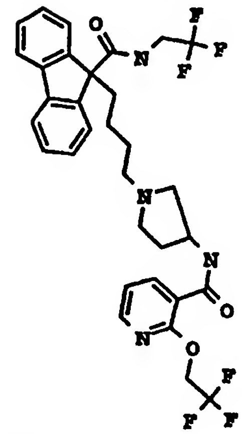

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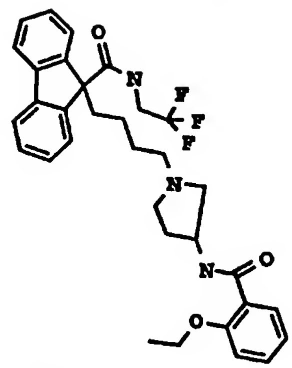

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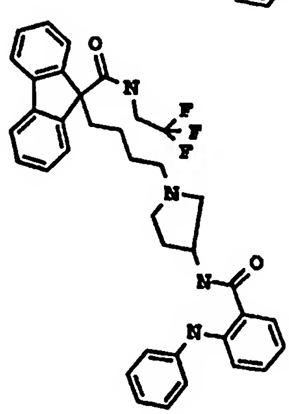
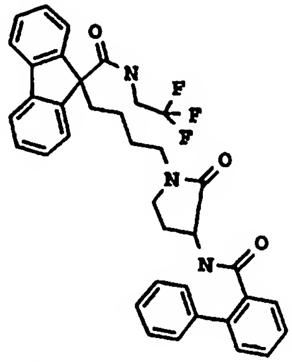
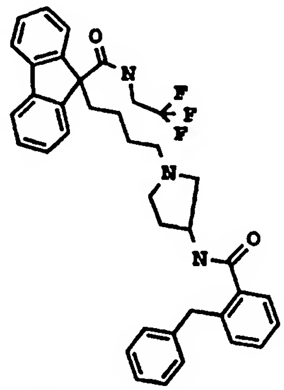
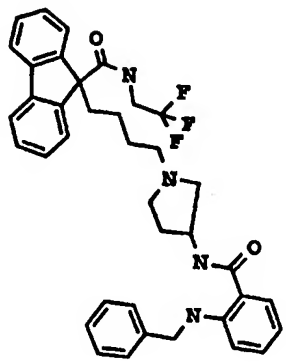
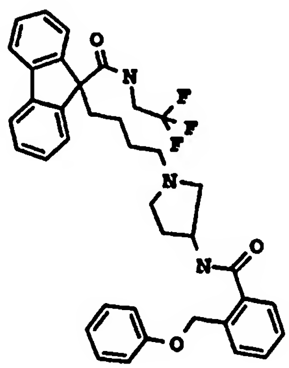


416 

417 

418 

419 

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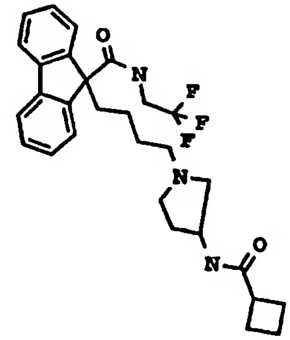

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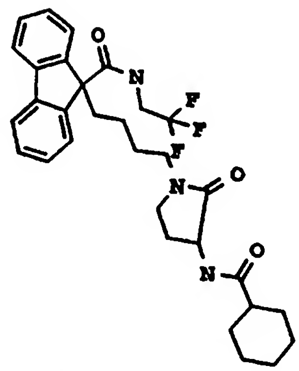

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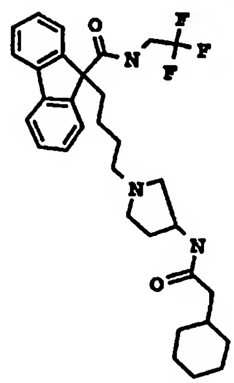

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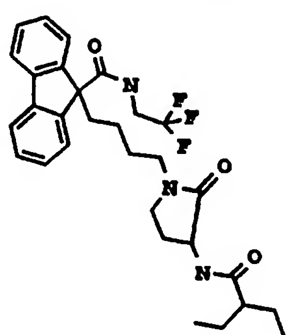
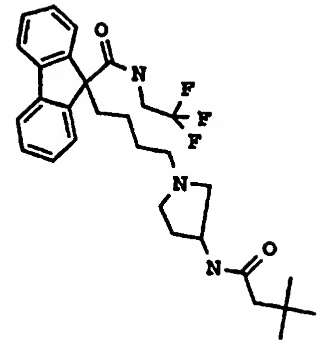
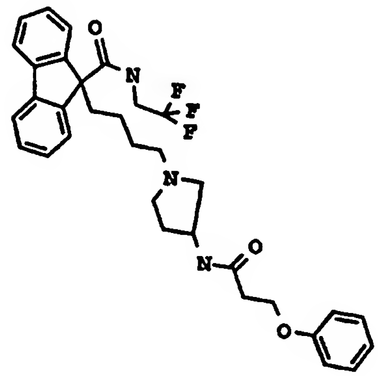
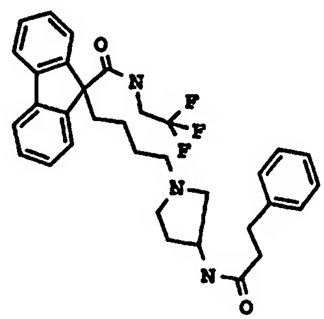
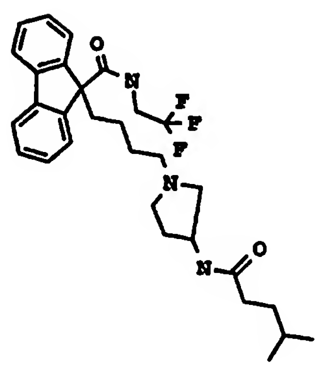


424 

425 

426 

427 

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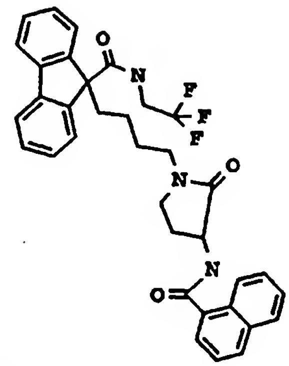

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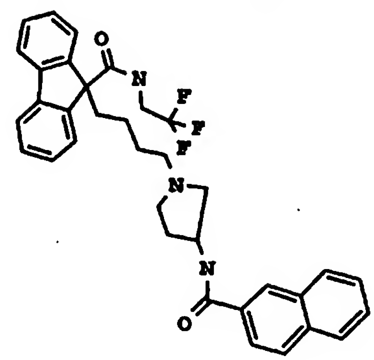

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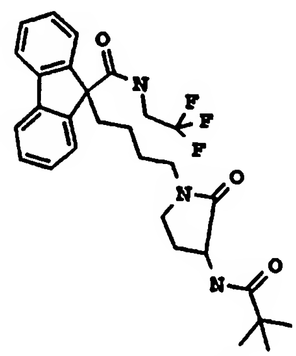

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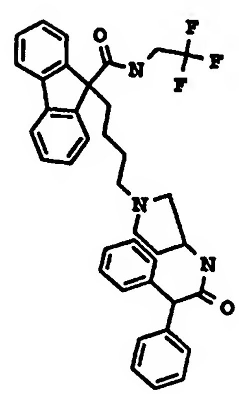

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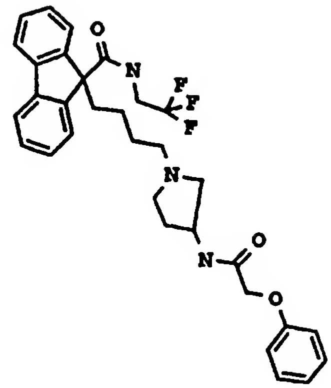


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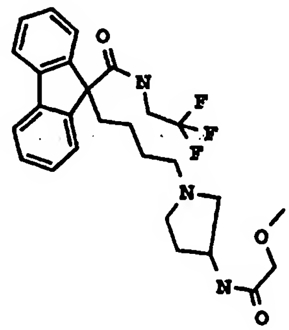


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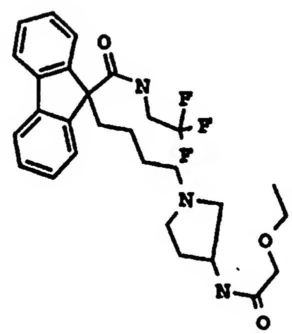


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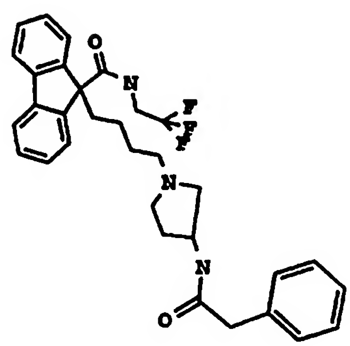

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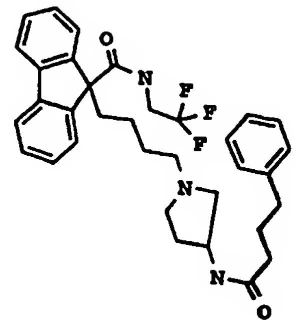

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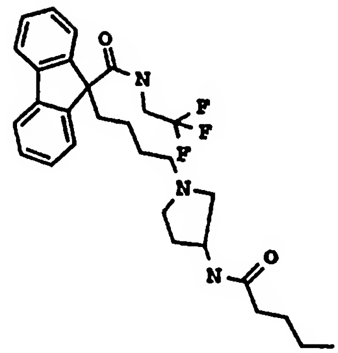

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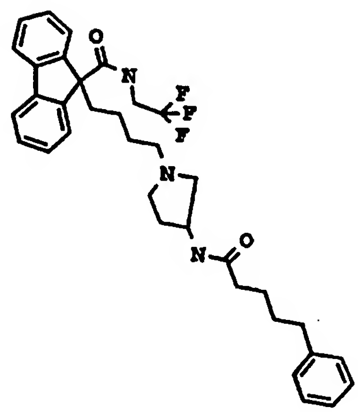

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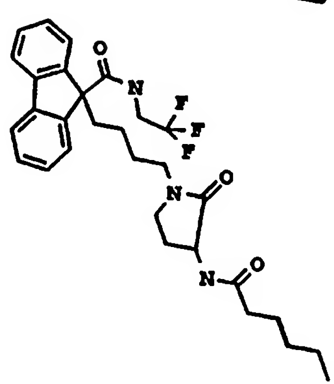

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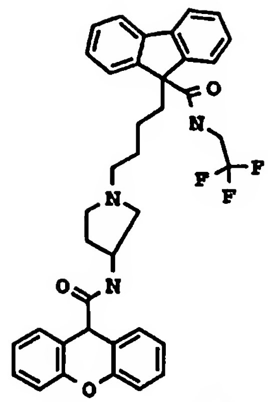

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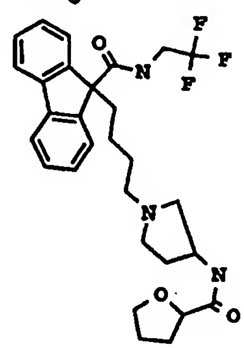

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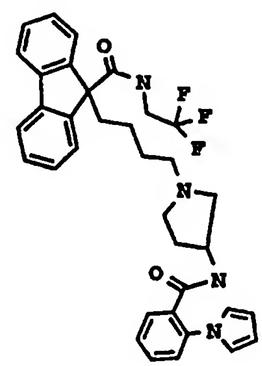

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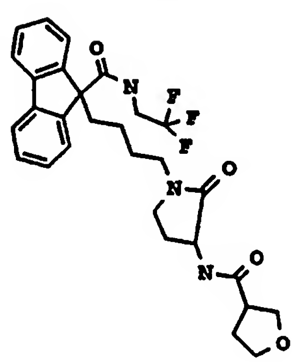

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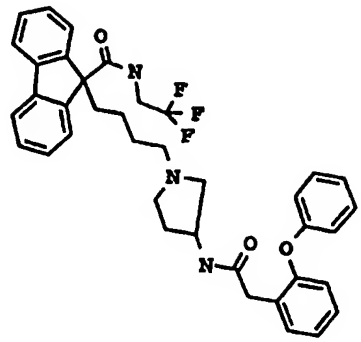

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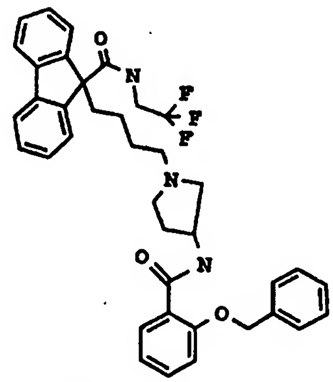

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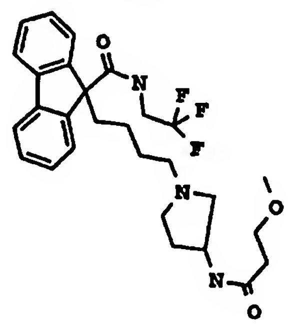

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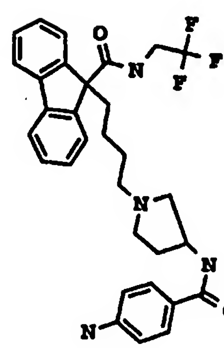
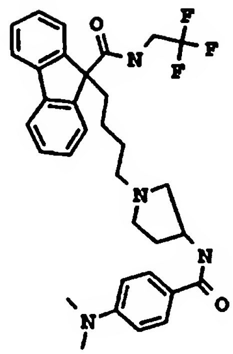
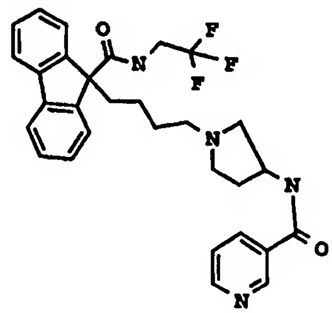
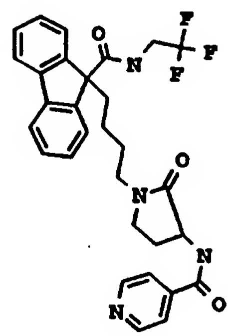
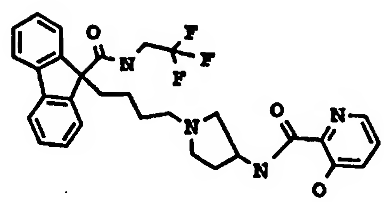
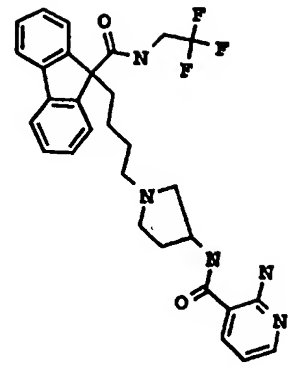


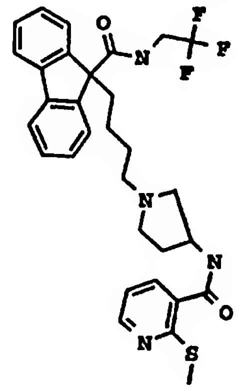
448 

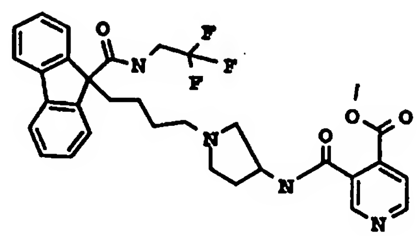
449 

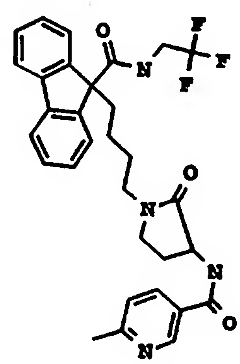
450 

451 

452 

453 

454 

455 

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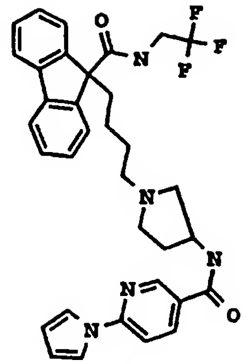

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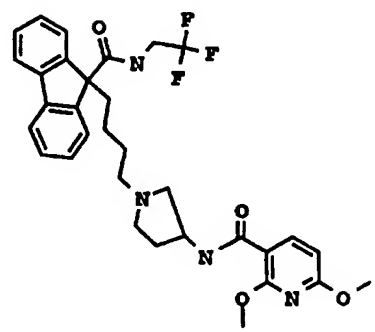

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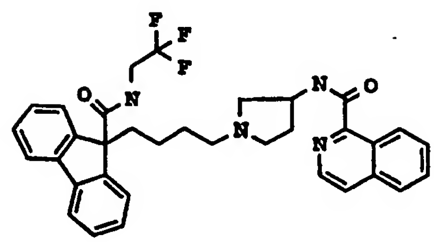

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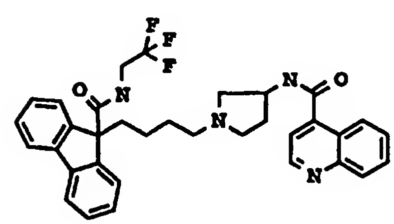

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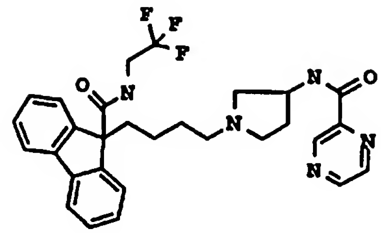

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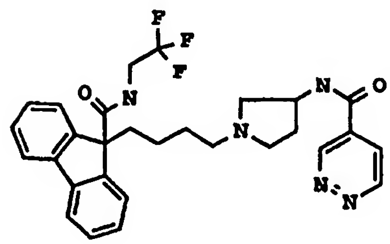

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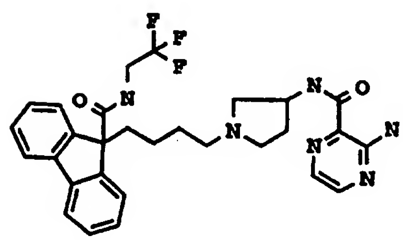

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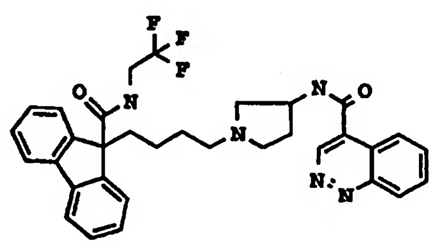

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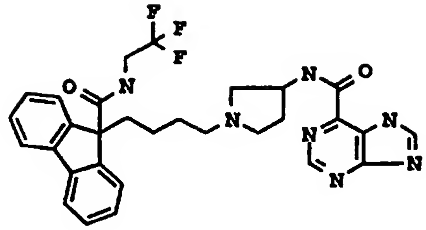

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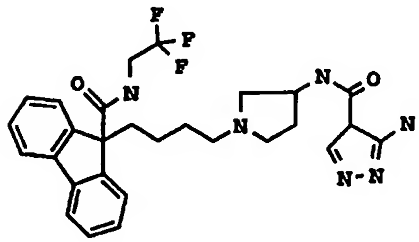

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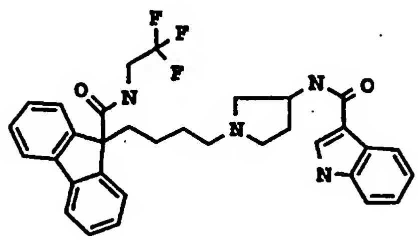

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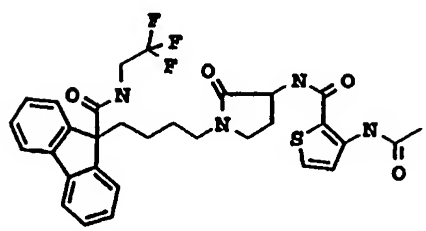

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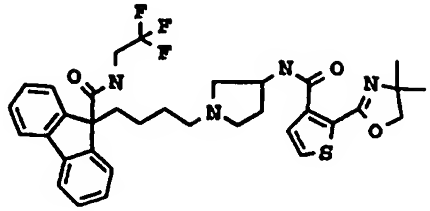

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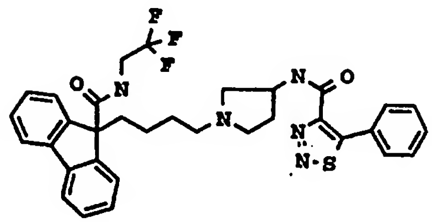

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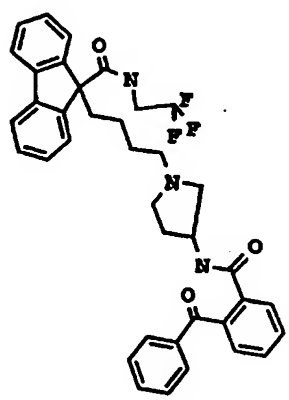

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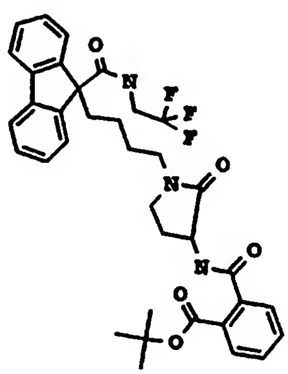

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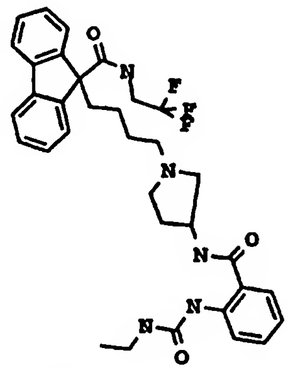

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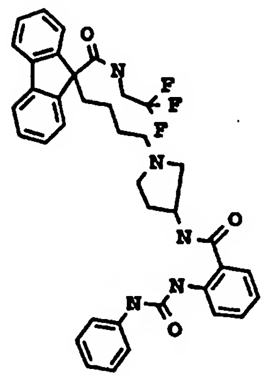

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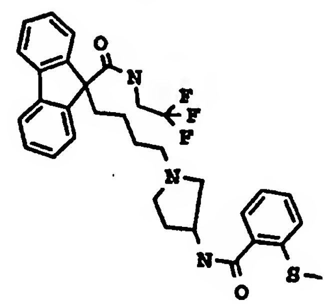

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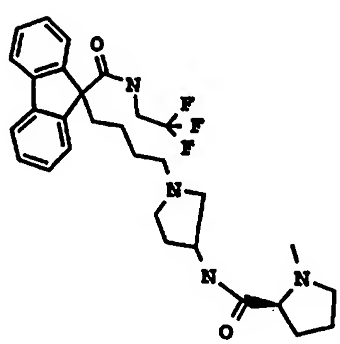


Example 476

9-[4-[3-[(Phenoxycarbonyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

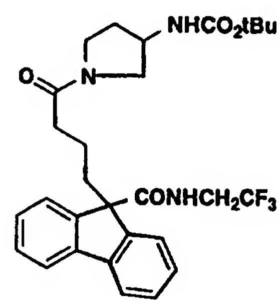
**Example 477**

9-[4-[3-[[(Phenylamino)carbonyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

**Example 478**

9-[4-[3-[(Phenylsulfonyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

**Example 479**



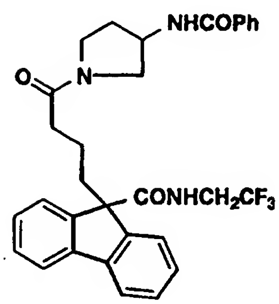

**Example 480**

cis-9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N-oxide

**Example 481**

9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-4-oxobutyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

**Example 482**



**Example 483**

9-[4-[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-1-pyrrolidinyl]pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

**Example 484**

9-[4-[3-[[(2-Phenoxyphenyl)sulfonyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

**Example 485**

[1-[[[2-[9-[[(2,2,2-Trifluoroethyl)amino)carbonyl]-9H-fluoren-9-yl]ethyl]amino]carbonyl]-3-pyrrolidin-yl]carbamic acid, 1,1-dimethylethyl ester

**Example 486**

9-[2-[[[3-(Benzoylamino)-1-pyrrolidinyl]carbonyl]-amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

**Example 487**

3-[[(1,1-Dimethylethoxy)carbonyl]amino]-1-pyrrolidinecarboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl], ethyl ester

**Example 488**

3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidine-carboxylicacid, 2-[9-[[(2,2,2-trifluoroethyl)-amino]carbonyl]-9H-fluoren-9-yl]ethyl ester

**Example 489**

9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

**Example 490**

9-[2-[[[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]carbonyl]amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

**Example 491**

3-(Benzoylamino)-1-pyrrolidinecarboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl ester

**Example 492**

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

**Example 493**

9-[4-[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide

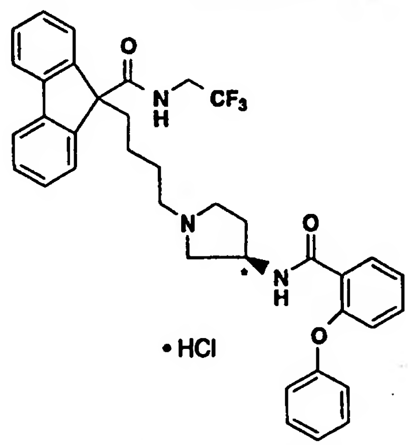
**Example 494**

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide

Example 495

9-[4-[3-[[(2-Phenoxyphenyl)carbonyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide

Example 496



R isomer

(R)-9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

m.p. 112-115°C

MS (ES, + ions): m/z 628 (M+H)

Anal. Calcd for $C_{37}H_{36}F_3N_3O_3$ + 1.0 HCl + 0.9 $H_2O$:

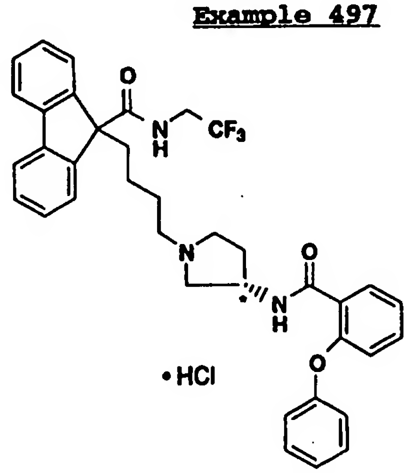
C, 65.32; H, 5.75; N, 6.18; F, 8.38;

Cl, 5.21

Found: C, 65.30; H, 5.59; N, 6.01; F, 8.83;

Cl, 5.35.

Example 497



S isomer

(S)-9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

m.p. 98-103°C

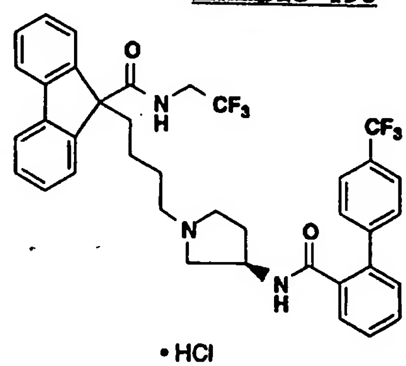
MS (ES, + ions): m/z 628 (M+H).

Anal. Calcd for $C_{37}H_{36}F_3N_3O_3$ + 1.0 HCl + 1.5 $H_2O$:

C, 64.30; H, 5.83; N, 6.08; F, 8.25

Found: C, 64.34; H, 5.63; N, 5.90; F, 8.46.

**Example 498**



R isomer

(R)-N-(2,2,2-Trifluoroethyl)-9-[4-[3-[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

m.p. 108-112°C

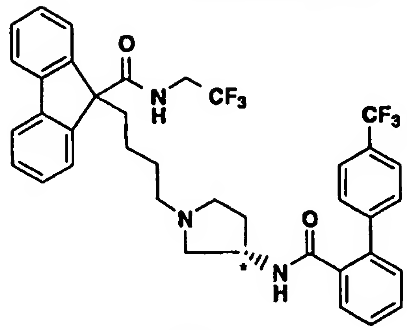
MS (ES, + ions): m/z 680 (M+H)

Anal. Calcd for $C_{38}H_{35}F_6N_3O_2$ + 1.3 HCl + 2.1 $H_2O$:

C, 59.67; H, 5.34; N, 5.49; Cl, 6.03

Found: C, 59.75; H, 5.00; N, 5.18; Cl, 5.75.

**Example 499**



• HCl

S isomer

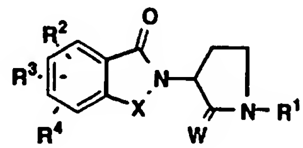
(S)-N-(2,2,2-Trifluoroethyl)-9-[4-[3-[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

m.p. 101-105°C

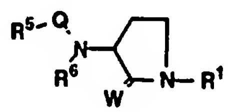
MS (ES, + ions): m/z 680 (M+H).

**What Is Claimed Is:**

1. A compound which has the structure



or



,

where Q is $-\overset{O}{\overset{\|}{C}}-$ or $-\underset{\underset{O}{\|}}{\overset{O}{\overset{\|}{S}}}-$ ;

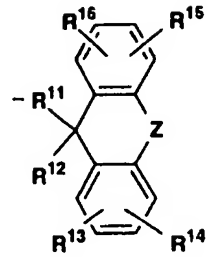
W is H,H or O;

X is: $CHR^8$, $-\underset{\underset{O}{\|}}{C}-$ , $-\underset{R^9}{\underset{|}{CH}}-\underset{R^{10}}{\underset{|}{CH}}-$ or $-\underset{R^9}{\underset{|}{C}}=\underset{R^{10}}{\underset{|}{C}}-$;

$R^8$, $R^9$ and $R^{10}$ are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

$R^1$ is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

or $R^1$ is a fluorenyl-type group of the structure



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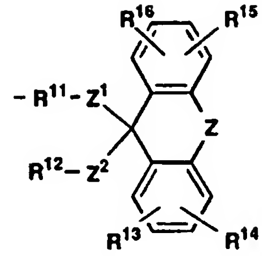

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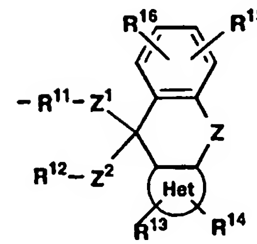
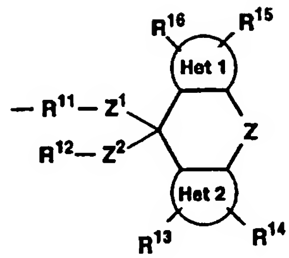


A B C

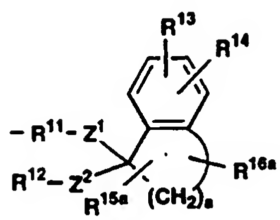
or



; or

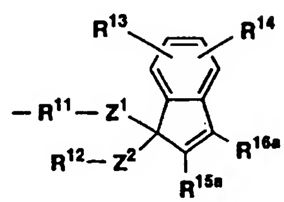
D

$R^1$ is an indenyl-type group of the structure



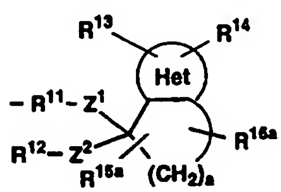
E (a = 2,3 or 4)

or



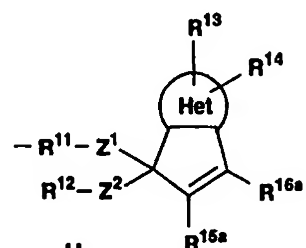
F

or



G

or



H

;

$Z^1$ and $Z^2$ are the same or different and are independently a bond, O, S,

$\underset{\|}{\overset{}{S}}{=}O$ , $S(O)_2$ , $-NH-\overset{O}{\overset{\|}{C}}-$ , $-N(\text{alkyl})-\overset{O}{\overset{\|}{C}}-$ , $-\overset{O}{\overset{\|}{C}}-$ or $-\underset{OH}{\overset{H}{C}}-$ ,

with the proviso that with respect to B, at least one of $Z^1$ and $Z^2$ will be other than a bond; $R^{11}$ is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; $R^{12}$ is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

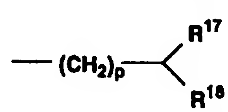
(1) when $R^{12}$ is H, aryloxy, alkoxy or arylalkoxy, then $Z^2$ is $-NH-\overset{\overset{\displaystyle O}{\|}}{C}-$ , $-\underset{\underset{\text{alkyl}}{|}}{N}-\overset{\overset{\displaystyle O}{\|}}{C}-$ , $-\overset{\overset{\displaystyle O}{\|}}{C}-$ or a bond and

(2) when $Z^2$ is a bond, $R^{12}$ cannot be heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; $R^{13}$, $R^{14}$, $R^{15}$, and $R^{16}$ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

$R^{15a}$ and $R^{16a}$ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

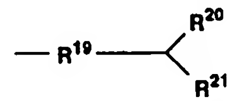
or $R^1$ is a group of the structure



wherein p is 1 to 8 and $R^{17}$ and $R^{18}$ are each independently H, alkyl, alkenyl, aryl, arylalkyl,

heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of $R^{17}$ and $R^{18}$ being other than H;

or $R^1$ is a group of the structure



wherein $R^{19}$ is aryl or heteroaryl;

$R^{20}$ is aryl or heteroaryl;

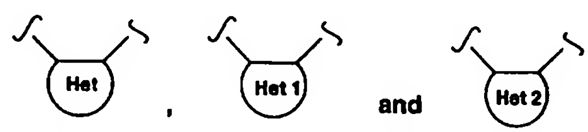
$R^{21}$ is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

$R^2$, $R^3$, $R^4$ are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

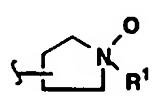
$R^5$ is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio,

arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylamino-carbonyl, alkylaminocarbonyl, alkenylamino-carbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroaryl-sulfonyl, alkylsulfinyl;

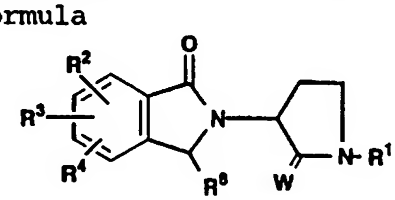
$R^6$ is hydrogen or $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkenyl; all optionally substituted with 1, 2, 3 or 4 groups which may independently be any of the substituents listed in the definition of $R^5$ set out above;



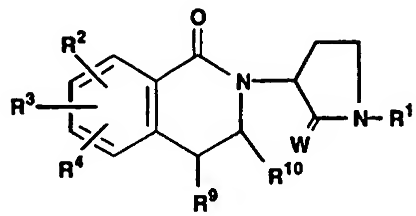

are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

an N-oxide  thereof; stereoisomers thereof; and a pharmaceutically acceptable salt thereof.

2. The compound as defined in Claim 1 having the formula



or



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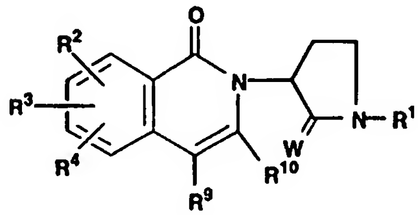
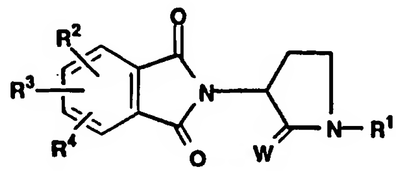
or



,

or

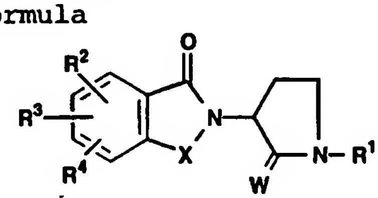


,

or

an N-oxide  thereof, and a pharmaceutically acceptable salt thereof.

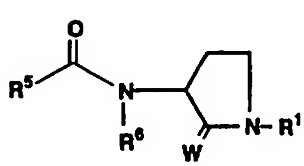
3. The compound as defined in Claim 1 having the formula



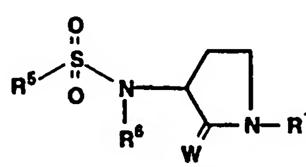
.

4. The compound as defined in Claim 3 where $R^1$ is arylalkyl, heteroalkylalkyl or cycloalkyl-alkyl.

5. The compound as defined in Claim 1 having the formula

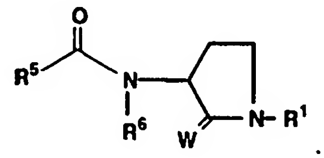


or

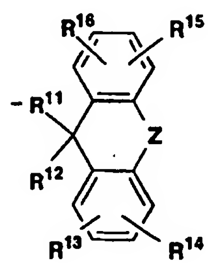


.

6. The compound as defined in Claim 1 having the formula

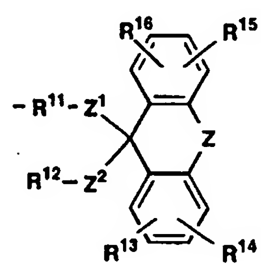


7. The compound as defined in Claim 1 wherein $R^1$ is



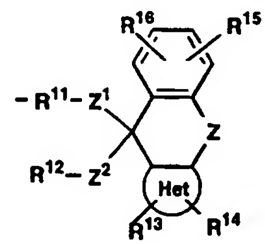
A

or



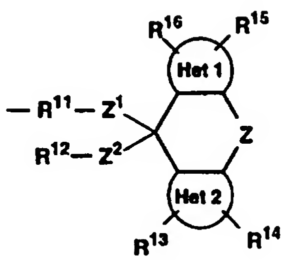
B

or



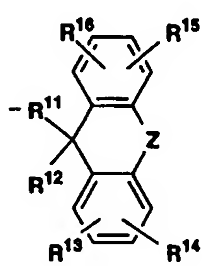
C

or



D

8. The compound as defined in Claim 7 wherein $R^1$ is



A

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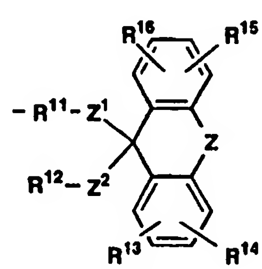


B

Z is a bond, O or S;

$R^{13}$, $R^{14}$, $R^{15}$ and $R^{16}$ are each H or one of $R^{15}$ and $R^{16}$ and one of $R^{13}$ and $R^{14}$ are halogen;

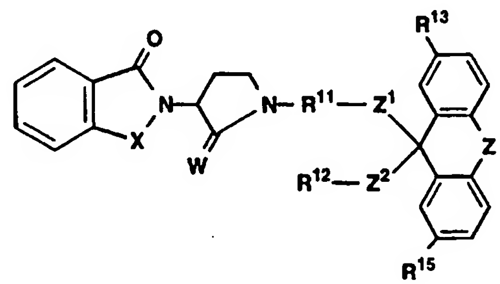
$Z^1$ is a bond or C=O;

$R^{11}$ is alkylene or alkenylene;

$R^{12}$ - $Z^2$ is $R^{12a}-NH-\overset{O}{\overset{\|}{C}}-$ ; or $R^{12a}\overset{O}{\overset{\|}{C}}-$ ;

$R^{12a}$ is alkyl, fluorinated lower alkyl or polyfluorinated lower alkyl.

9. The compound as defined in Claim 1 having the structure



Z is O, S or a bond;

$R^{13}$ and $R^{15}$ are independently H or F;

$Z^1$ is a bond;

$R^{11}$ is alkylene;

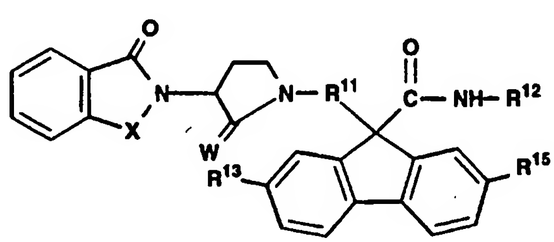
$R^{12}$-$Z^2$ is $\text{alkyl}-NH-\overset{O}{\overset{\|}{C}}-$ or $R^{12a}-NH\overset{O}{\overset{\|}{C}}-$ ; and

$R^{12a}$ is alkyl, fluorinated lower alkyl or polyfluorinated lower alkyl.

10. The compound as defined in Claim 9 wherein $R^{11}$ is $-(CH_2)_4-$, $Z^1$ is a bond, and $R^{12}$-$Z^2$ is

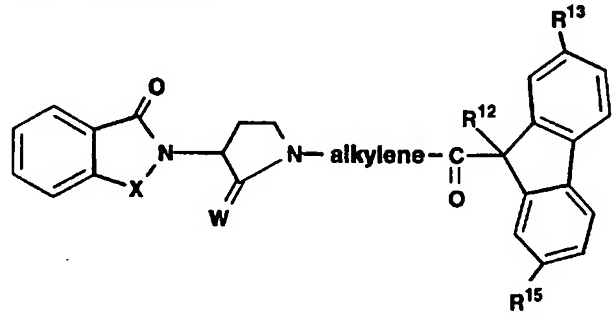
$CH_3(CH_2)_2-\underset{H}{N}-\overset{O}{\overset{\|}{C}}-$ or $CF_3CH_2-\underset{H}{N}-\overset{O}{\overset{\|}{C}}-$ .

11. The compound as defined in Claim 9 having the structure



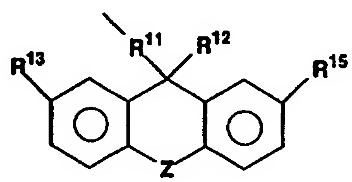
where $R^{13}$ and $R^{15}$ are independently H or F, and $R^{12}$ is trifluoromethylalkyl or alkyl.

12. The compound as defined in Claim 9 having the structure

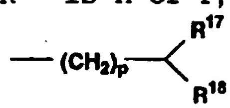


where $R^{12}$ is alkyl, and $R^{13}$ and $R^{15}$ are independently H or F.

13. The compound as defined in Claim 1 wherein $R^1$ is arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl,

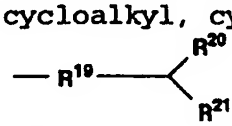


where $R^{11}$ is alkylene or alkenylene; $R^{12}$ is H, alkyl, alkenyl, aralkyl, aralkenyl; and $R^{13}$ is H or F; and $R^{15}$ is H or F; Z is O, S or a bond; or $R^1$ is



wherein $(CH_2)_p$ represents an alkylene chain or cis alkenylene of up to 6 carbons;

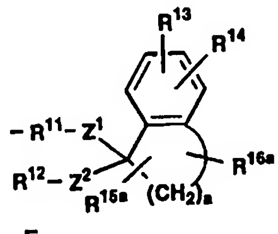
$R^{17}$ and $R^{18}$ are each independently alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroaryl-alkyl, cycloalkyl, cycloalkylalkyl; or $R^1$ is



$R^{19}$ is aryl or heteroaryl; $R^{20}$ is aryl or heteroaryl;

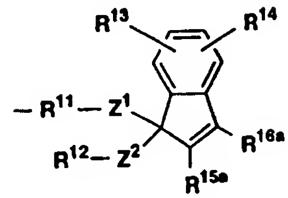
$R^{21}$ is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl, or cycloalkylalkoxy.

14. The compound as defined in Claim 1 wherein $R^1$ is an indenyl-type group of the structure



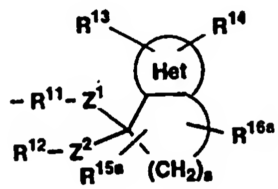
E (a = 2,3 or 4)

or



F

or



G

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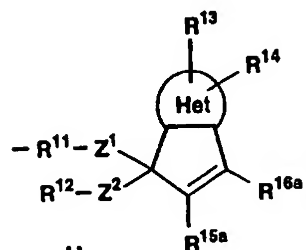
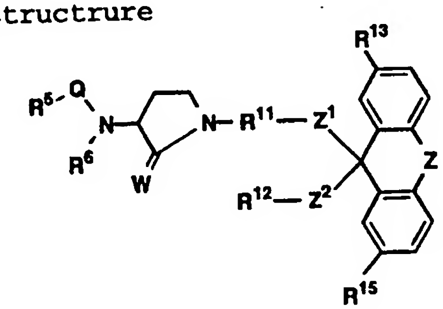
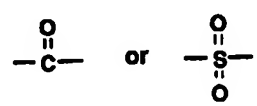


H.

15. The compound as defined in Claim 1 having the structrure



where Q is  ;

Z is a bond, O or S;

where $R^5$ is cycloalkyl, phenyl, aryl, heteroaryl, or cycloalkyl, phenyl, aryl or heteroaryl, independently substituted at the ortho position with alkyl, alkoxy, haloalkyl (optionally substituted with up to 5 halogens), trifluoromethyl, aryl, aryloxy, haloalkoxy (optionally

substituted with up to 5 halogens), arylalkyl or arylalkoxy;

$R^6$ is H or $CH_3$;

$R^{13}$ and $R^{15}$ are independently H or F;

$Z^1$ is a bond;

$R^{11}$ is alkylene;

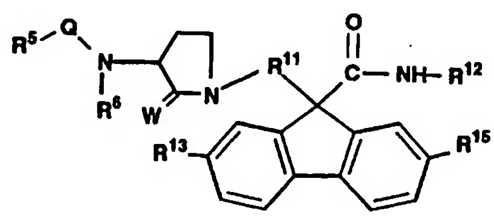
$R^{12} - Z^2$ is $\text{alkyl}-NH-\overset{O}{\overset{\|}{C}}-$ or $CF_3\text{alkyl}NH\overset{O}{\overset{\|}{C}}-$,

or $Z^2$ is a bond and $R^{12}$ is alkyl.

16. The compound as defined in Claim 15 wherein $R^{11}$ is $-(CH_2)_4-$, $Z^1$ is a bond, and $R^{12}-Z^2$ is

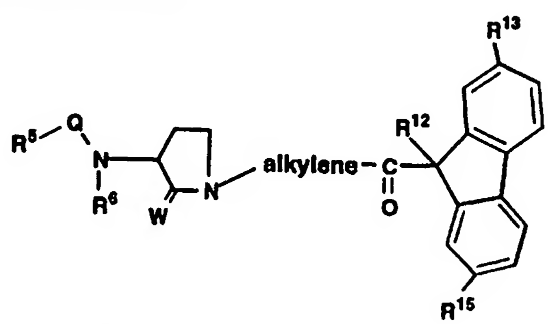
$CH_3(CH_2)_2-\underset{H}{N}-\overset{O}{\overset{\|}{C}}-$ or $CF_3CH_2-\underset{H}{N}-\overset{O}{\overset{\|}{C}}-$.

17. The compound as defined in Claim 15 having the structure



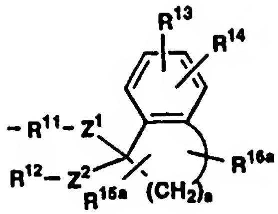

and $R^{12}$ is trifluoromethylalkyl or alkyl.

18. The compound as defined in Claim 15 having the structure

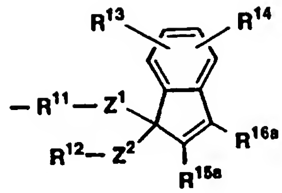



where $R^{12}$ is alkyl.

19. The compound as defined in Claim 1 wherein $R^1$ is a group of the structure

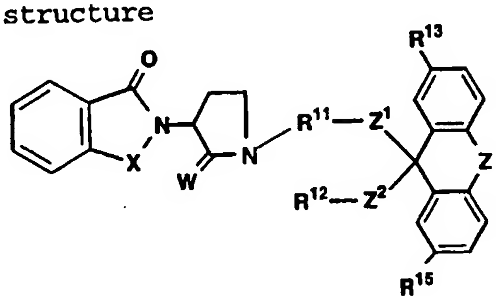


or



E (a = 2,3 or 4) F

20. The compound as defined in Claim 1 having the structure

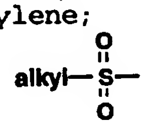


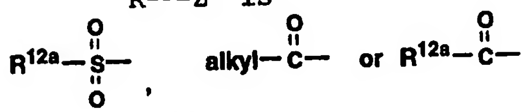
Z is O, S or a bond;

$R^{13}$ and $R^{15}$ are independently H or F;

$Z^1$ is a bond;

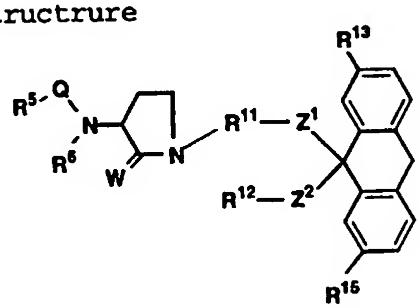
$R^{11}$ is alkylene;

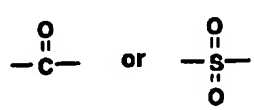
$R^{12}$-$Z^2$ is  ,

 ; and

$R^{12a}$ is alkyl, fluorinated lower alkyl or polyfluorinated lower alkyl.

21. The compound as defined in Claim 1 having the structrure



where Q is  ;

Z is a bond, O or S;

where $R^5$ is cycloalkyl, phenyl, aryl, heteroaryl, or cycloalkyl, phenyl, aryl or heteroaryl, independently substituted at the ortho position with alkyl, alkoxy, haloalkyl (optionally substituted with up to 5 halogens), trifluoromethyl, aryl, aryloxy, haloalkoxy (optionally substituted with up to 5 halogens), arylalkyl or arylalkoxy;

$R^6$ is H or $CH_3$;

$R^{13}$ and $R^{15}$ are independently H or F;

$Z^1$ is a bond;

$R^{11}$ is alkylene;

$R^{12}$ - $Z^2$ is $\text{alkyl}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-$ , $R^{12a}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-$ , $\text{alkyl}-\overset{\overset{\displaystyle O}{\|}}{C}-$ or $R^{12a}-\overset{\overset{\displaystyle O}{\|}}{C}-$ ,

$R^{12a}$ is alkyl, fluorinated lower alkyl or polyfluorinated lower alkyl,

or $Z^2$ is a bond and $R^{12}$ is alkyl.

22. The compound as defined in Claim 1 which is

9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

9-[4-[3-(benzoylamino)-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

(R)-9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

(S)-9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

(R)-N-(2,2,2-trifluoroethyl)-9-[4-[3-[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-

yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide,

(S)-N-(2,2,2-trifluoroethyl)-9-[4-[3-[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]-carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide,

9-[4-[2-oxo-3-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

9-[4-[3-[[2-(2-benzothiazolyl)benzoyl]-amino]-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

9-[4-[2-oxo-3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

9-[4-[3-(benzoylamino)-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

9-[4-[2-oxo-3-[[2-(2-pyridinyl)benzoyl]-amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoro-ethyl)-9H-fluorene-9-carboxamide, or

9-[4-[3-[[2-(4-morpholinyl)benzoyl]amino]-2-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

or a pharmaceutically acceptable salt thereof.

23. A method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

24. A method of lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

## INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/07603

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/309, 417, 418, 419, 423, 424; 546/141; 548/472, 473, 484, 485, 486, 528, 530, 532, 533

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 5,416,009 A (HARTMAN et al.) 16 May 1995, columns 2-4, entire discloser. | 1-24 |
| A | US 5,362,736 A (ISHIKAWA et al.) 08 November 1994, column 1, formula I. | 1-24 |
| A | US 5,304,556 A (YAMAMOTO et al.) 19 April 1994, column 2, compound of formula (I), line 60. | 1-24 |
| A | US 4,459,414 A (FISCHER et al.) 10 July 1984, entire discloser in columns 1 and 2. | 1-24 |
| A | US 3,740,415 A (KASHIHARA et al.) 19 June 1973, columns 1 and 2. | 1-24 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
01 JULY 1997

Date of mailing of the international search report
24 JUL 1997

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**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/US97/07603

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/07603

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 207/12, 209/12, 209/34, 217/24, 401/04; A61K 31/405, 31/47, 31/395

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/309, 417, 418, 419, 423, 424; 546/141; 548/472, 473, 484, 485, 486, 528, 530, 532, 533

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-4, 7-14, 19, 20 and 22-24, drawn to mixed heterocyclic compounds.

Group II, claims 1, 2, 5-8, 13-19 and 21-24, drawn to pyrrolidine compounds.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The compounds of inventions I and II are drawn to structurally dissimilar compounds. They are made and used independently. They are independent. If, say, invention of Group I, the mixed heterocyclic compounds, were anticipated, applicants would not acquiesce in objection of Group II compounds there over or vice-versa. They inventions of Groups I and II are distinct.